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Novel Treatment for the Prevention of Secondary Adhesions

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Abstract

Adhesion formation following surgical procedures poses a major clinical challenge, often leading to chronic pain, increased hospital readmissions, and substantial healthcare costs exceeding a billion dollars annually. Despite advancements in surgical techniques, minimally invasive approaches, and barrier methods, there is a lack of targeted research on preventing secondary adhesions after adhesiolysis. This study aims to bridge this gap in the literature by exploring novel treatment options. In our earlier research, alanyl-glutamine was shown to effectively prevent primary adhesions in a rat model involving polypropylene-type meshes, which are typically associated with severe adhesions despite their suitability for hernia repair. Building on these findings, we extended our investigation to determine if this treatment could also prevent secondary adhesions post-adhesiolysis. In this study, adhesions were induced in Wistar rats, followed by adhesiolysis and subsequent treatment with alanyl-glutamine. Six weeks post-treatment, the extent of adhesion formation was evaluated, revealing no adhesion formation. Our results demonstrate that alanyl-glutamine effectively prevents both primary and secondary adhesions in a rat model, highlighting its potential as a promising intervention to mitigate the adverse effects and complications associated with surgical adhesions.

Keywords: Adhesions, Secondary adhesions, Adhesiolysis, Alanyl-glutamine, Abdominal surgery, Secondary adhesion prevention

Introduction/Background Literature

Secondary adhesions are adhesion which develop after surgery it could also occur after a previous adhesiolysis procedure, are a major cause of patient readmission, costing the healthcare system over 2 billion dollars annually.[1,2] The economic burden includes expenses related to repeat surgeries, extended hospital stays, and managing complications from adhesions.

Adhesions often result in distressing conditions such as chronic abdominal and pelvic pain, small bowel obstruction, infertility, and reduced mobility. Repeat adhesiolysis puts patients at risk of further surgeries, creating a cycle of physical, mental, and financial strain.[3-5] These surgeries typically require longer operative times[6] and increases the occurrence of anesthetic complications, hospital-acquired infections, and other risks associated with prolonged hospital stays.

Adhesions can arise from various causes, with post-surgical cases accounting for 90%. They also occur following infectious and inflammatory processes, such as endometriosis and pelvic inflammatory disease, and post-radiation therapy. Adhesions can also be congenital, transitory, and asymptomatic. While non-operative methods like deep tissue massage and stretching exercises are recommended to manage adhesion complications, adhesiolysis remains the definitive treatment with studies showing a reduction in adhesion recurrence compared to conservative management.[7,8] However, incomplete lysis, particularly in cases of matted adhesions, can lead to recurrent adhesive small bowel obstruction.[9] The risk of bowel injuries with each consecutive laparotomy can reach up to 50%, leading to higher postoperative mortality and increased healthcare costs, especially when bowel injury occurs during adhesiolysis.[10]

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Adhesion formation is influenced by several factors, including the complexity of the operation, the degree of peritoneal trauma, pre-existing illnesses (such as diabetes), poor nutritional status,[11] the use of meshes as in the case of ventral hernia repair,[12] excessive coagulation leading to tissue necrosis, and coexisting bacterial infections.[13] During laparoscopy, key contributors to adhesion formation include dehydration due to high insufflation pressure and mesothelial hypoxia caused by carbon dioxide use.[14] In laparotomy, factors such as dehydration from light and heat exposure, contact with foreign materials (such as glove powder), and abrasion from dry abdominal drapes also play significant roles in adhesion development.[15]

Various strategies are used to mitigate adhesion formation in high-risk surgeries, including barrier agents like oxidized regenerated cellulose (Interceed), polytetrafluoroethylene (PTFC) (Gore-Tex) and Seprafilm, along with gentle tissue handling, meticulous hemostasis, and minimizing tissue trauma through minimally invasive surgery (MIS) with laparoscopy/robotic techniques.[16,17] Despite these measures, adhesions still form irrespective of the method employed. To date, no studies in the literature have specifically addressed the reversal of secondary adhesions. This study aims to address this gap in knowledge.

Study aim

To evaluate effect of treatment with alanyl-glutamine on the reversal adhesion formation found after abdominal surgery Therefor preventing the formation secondary adhesion formation in a rat model.

Method

The study subjects were 24 Wistar rats weighing greater than 300g. All animals were anesthetized with halothane and given bupivacaine for post-procedure pain control. Laparotomy was done followed by cecal ligation and puncture (CLP), a commonly used method for reproducing sepsis in vivo.[18] The cecal puncture was immediately closed with a purse-string suture. Vicryl suture was used to close. The abdominal cavity was then irrigated to remove any possible fecal material that may have escaped from the cecum. The skin was stapled. After 30 days, laparotomy was repeated to evaluate for the presence of adhesions Figure 1. Adhesiolysis was performed, the novel treatment was infiltrated into the abdominal cavity, and the skin was stapled. Twelve rats received surgery and the treatment while twelve other rats received surgery only. Six rats with virgin abdomens did not receive surgery and were used as controls. Laparotomy was done 6weeks later and the abdomen was evaluated for secondary adhesions Figure 2.

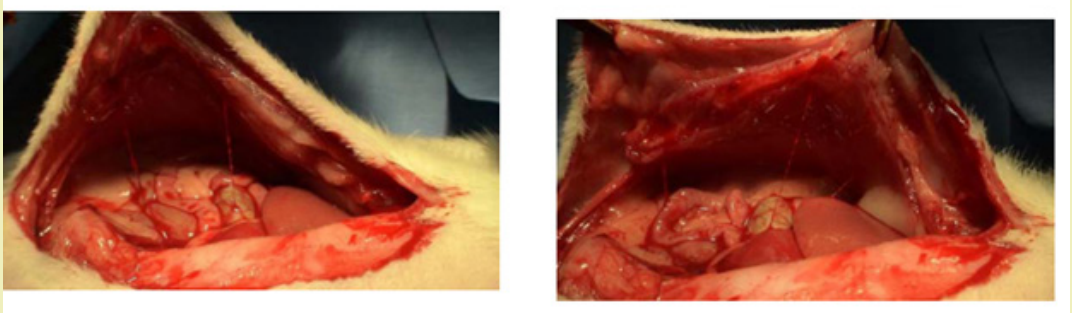

Figure 1: Primary adhesions seen 6 weeks post initial laparotomy

Approval for this study was received from the University of Saskatchewan Animal Ethics Board.

Results

Treatment group abdomens showed a lack of adhesions after alanyl- glutamine was placed post adhesiolysis. Abdomens without the treatment demonstrated adhesion formation. The novel adhesion treatment prevents formation of secondary adhesions after adhesiolysis in a rat model.

Discussion

Adhesion formation following abdominal surgery is a complex and multifaceted process. Adhesions develop as a result of the invasion of the peritoneum by circulating system cells, which gain access to the peritoneal cavity due to the increased availability of milky spots-small, lymphoid aggregates within the peritoneum that serve as entry points for immune cells.[19,20] This cellular invasion and subsequent inflammatory response lead to the formation of fibrous bands, which can cause complications such as bowel obstruction, chronic pain, and infertility. Our previous study explored the role of alanyl-glutamine (AG) in preventing primary adhesion formation. AG was shown to modulate the repair processes of the peritoneum and omentum by enhancing the function of mesothelial cells, macrophages, and fibroblasts. This modulation resulted in fewer milky spots being available for systemic monocytes and fibroblasts to infiltrate, thereby reducing adhesion formation. Our current findings extend these results, demonstrating AG's effectiveness in preventing secondary adhesion formation as well.

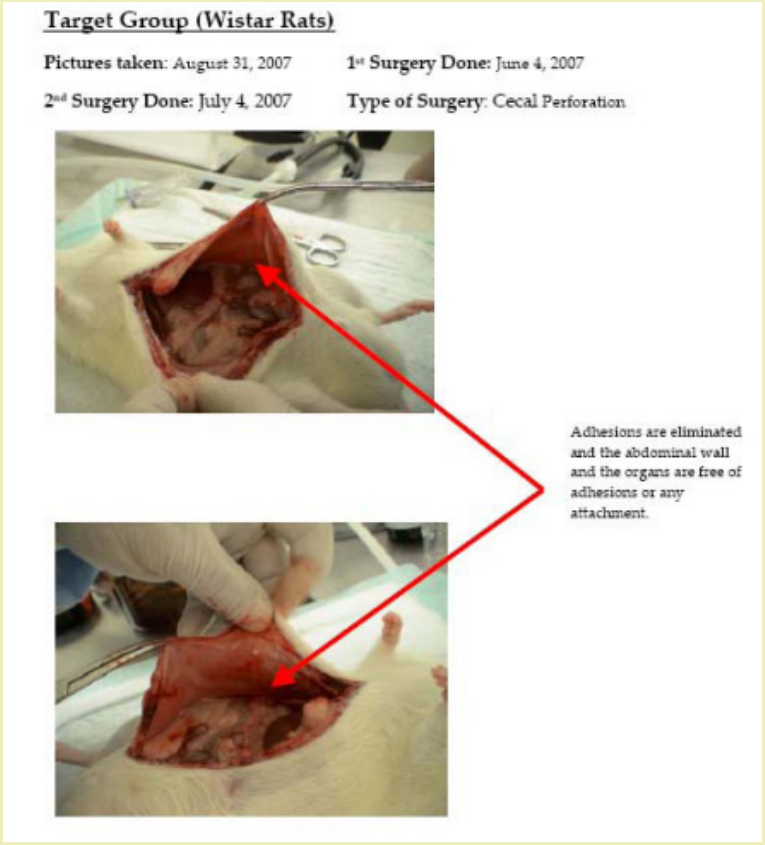

Figure 2: Six weeks post adhesiolysis and infiltration with alanyl glutamine, no secondary adhesions are seen

Mechanisms and comparison of anti-adhesion agents

Alanyl-glutamine works by enhancing the intrinsic repair mechanisms of the peritoneal lining. By supporting the functional capacity of mesothelial cells, which form the first line of defense against adhesion formation, AG helps maintain the integrity of the peritoneal barrier. Additionally, AG modulates macrophage activity, which is crucial for resolving inflammation and preventing excessive fibroblast proliferation-a key factor in adhesion formation.

When compared to traditional anti-adhesion agents such as hyaluronic acid–carboxymethylcellulose (Seprafilm), polydioxanone, or oxidized regenerated cellulose, AG has shown superior efficacy. These agents primarily function as physical barriers that temporarily prevent tissue surfaces from adhering to each other during the healing process. However, they do not actively engage in the modulation of cellular repair mechanisms. As a result, while they can be effective to a degree, their benefits are often limited to the period during which they remain in place.[21,22] In contrast, AG not only provides an immediate protective effect but also fosters a more favorable healing environment by actively supporting cellular repair and reducing inflammatory responses. This dual action makes AG a more comprehensive solution for adhesion prevention.

Economic and clinical implications

The cost-effectiveness of AG is another significant advantage. The financial burden of managing adhesion-related complications is substantial, with costs accumulating from prolonged hospital stays, repeated surgeries, and long-term management of chronic conditions[22,23] preventing both primary and secondary adhesions, AG can significantly reduce these expenses, presenting a financially sustainable option for healthcare systems. Moreover, improved patient outcomes are paramount. Adhesions can severely impact quality of life, causing pain, infertility, and repeated hospitalizations. By effectively preventing adhesion formation, AG contributes to better surgical outcomes and enhances overall patient well-being. The reduction in postoperative complications translates to faster recoveries and less strain on healthcare resources.

Conclusion

Secondary adhesion is the most common adhesion as it is mostly seen in patients had has previous abdominal surgery. Many current methods for preventing adhesions are not only ineffective but also costly, leaving patients to suffer from chronic pain and frequent hospital readmissions.[22] Our study shows that alanyl-glutamine plays a significant role in preventing adhesion formation. Alanyl-glutamine effectively prevents secondary adhesions by enhancing

the body's natural repair mechanisms. This makes it a valuable addition to surgical practice, with the potential to significantly improve patient care, reduce the complications of adhesions as well as its cost implications, and enhance the quality of life for those undergoing surgery. Moving forward, further research is essential to confirm its benefits in humans, with the goal of setting a new standard in adhesion prevention and ultimately improving health outcomes for patients worldwide.

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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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