Impact of magnesium on intraperitoneal adhesion in an experimental rat model

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Abstract

Background. Intraperitoneal adhesions are fibrous bands that form between tissues and organs in the abdominal cavity, which can result from the body's healing process after surgery, leading to pain, bowel obstruction, and infertility in severe cases. Magnesium (Mg), known for its anti-inflammatory and anticoagulant properties, has been hypothesized to influence adhesion formation.

Objectives. This study is designed to explore the hypothesized benefits of Mg, known for its anti-inflammatory and anticoagulant properties, on the prevention of intraperitoneal adhesions that commonly occur following abdominal surgeries. It seeks to provide a comprehensive understanding of Mg's potential role in mitigating adhesion formation, aiming to contribute valuable insights into postoperative recovery processes and outcomes.

Materials and methods. We employed an experimental model of intestinal abrasion in male Wistar rats. The rats were categorized into control and treatment groups, with the latter receiving varying doses of Mg sulfate. Intraperitoneal adhesions were induced using a multi-abrasion model.

Results. Based on both the Evans model and histopathological evaluations, it was observed that there were significant differences in adhesion scores between the groups. Magnesium-treated groups showed significantly fewer adhesions than the control group. Histopathological analyses indicated variations in adhesion characteristics and inflammatory responses among the groups.

Conclusions. Preliminary results indicated the potential role of Mg in mitigating postoperative intraperitoneal adhesions. These findings suggest the need for further research to confirm the efficacy of Mg and to explore its mechanisms of action in clinical settings.

Key words: intraperitoneal adhesion, anti-inflammatory agents, magnesium sulfate, adhesion prevention

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Background

Postoperative adhesions are fibrovascular bands that form between peritoneal surfaces, usually occurring after abdominal or pelvic surgeries, with a reported incidence of up to 54%.[1,2] These adhesions develop as part of the natural healing process, involving factors such as coagulation, inflammation and fibrinolysis, and their clinical significance varies.[3] Despite advances in surgical techniques, peritoneal adhesions remain a significant clinical challenge, often necessitating further intervention. While not classified as complications, adhesions can lead to various issues in approx. 19% of patients, including acute/chronic abdominal pain, bowel obstruction, infertility, and iatrogenic intestinal injury during adhesiolysis.[2,4]

Magnesium (Mg), the 4th most abundant mineral in the human body, serves as a cofactor in more than 300 enzymatic reactions and influences energy metabolism, protein synthesis and nucleic acid synthesis.[5–7] Moreover, its anti-inflammatory,[8–14] antioxidant,[11,15] bronchodilator,[16] vasodilator,[17,18] antiaggregant,[19] and neuroprotective[20,21] properties have been demonstrated. These properties are linked to reduced anesthesia requirements during surgery[22] and are effective at controlling neuropathic pain.[23]

The inflammatory process and fibrin matrix formation following peritoneal injury are major factors responsible for adhesion formation,[3] and the anti-inflammatory and coagulation-related effects of Mg have been demonstrated in many studies.

Objectives

Given Mg's well-known effects on the inflammatory and coagulation cascades, this study aimed to investigate the effect of Mg on intra-abdominal adhesions in an experimental intestinal abrasion rat model.

Materials and methods

Study design

Twenty-six male Wistar albino rats, aged 9–10 weeks and weighing 300–400 g, were obtained from the Experimental Animals Research Unit of the Bülent Ecevit University, Zonguldak, Turkey. The rats were allowed to acclimate under standard laboratory conditions, namely, 23 ±2°C, 50% humidity and a 12-h artificial light cycle, for 1 week. Throughout this period, the animals had ad libitum access to food and water.

Magnesium sulfate ($MgSO_4$) (15%; Biofarma, Istanbul, Turkey) was utilized in the experimental procedures.

This study was conducted in line with the ethical standards set by the National Institutes of Health Guidelines for the care and use of laboratory animals. Approval for the study was obtained from the Ethics Review Board of the Zonguldak Bulent Ecevit University (Zonguldak, Turkey; protocol No. 2021-20-02/09).

Multi-abrasion model

The intra-abdominal adhesion model described by Öncel et al. was used in this study.[24] A 12-mm incision was made in the midline to reveal the cecum and small intestine. The anterior wall of the cecum was gently abraded with 20 strokes using a brush. During this procedure, the soft motion of the brush carefully abraded the surface of the organ wall. Additionally, 5 abrasions were induced on the small intestine at intervals of 3 cm, starting 5 cm from the ileocecal valve, as illustrated in Fig. 1. Following the creation of the abrasions, the cecum and small intestine were repositioned. The abdominal incision was closed in 2 layers using 3-0 polyglactin and 3-0 polypropylene sutures.

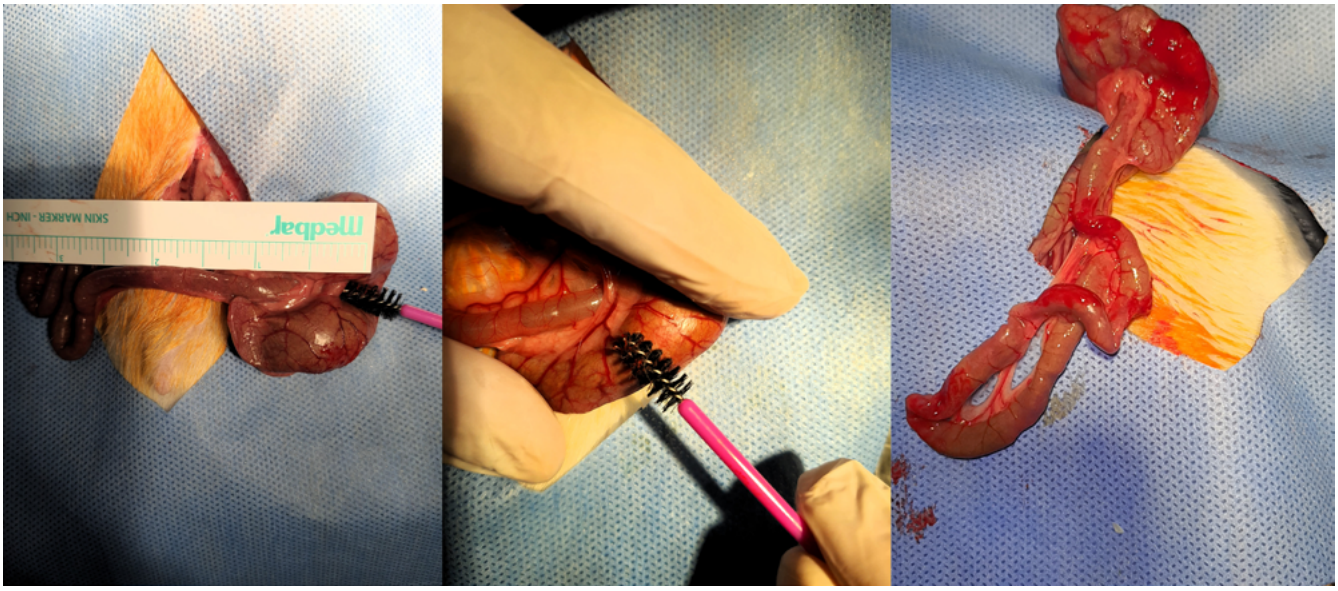

Fig. 1. Illustration of the intra-abdominal adhesion model as implemented by Öncel et al.[24]

Surgical procedure

The rats were randomly assigned to 1 of the following 4 groups: group 1 (sham group, n = 2), group 2 (control group, n = 8), group 3 (300 mg/kg $MgSO_4$ treatment group, n = 8), and group 4 (500 mg/kg $MgSO_4$ treatment group, n = 8).

The rats were weighed and then anesthetized using an intramuscular injection of 100 mg/kg ketamine (Ketalar; Parke Davis Eczacıbaşı, Istanbul, Turkey). The lower abdomen was shaved and cleaned with alcohol and povidone-iodine. All surgical procedures were performed in a semi-sterile environment by the same surgeon.

Rats in group 1 did not undergo surgery. Rats in groups 2, 3 and 4 were subjected to the multi-abrasion model, as detailed by Öncel et al.[24] For groups 3 and 4, before the abdominal cavity was closed, $MgSO_4$ in proportion to their body weight was intraperitoneally administered. After the surgery, each animal was placed in an individual cage. Rats were provided standard food and had adequate access to water; they were euthanized on post-operative day 7. Laparotomy was conducted to evaluate adhesion formation using a validated adhesion scoring system. Adhesions were assessed and graded according to the Evans model[25] (Table 1). An observer blinded to the study design performed the scoring process, as shown in Fig. 2,3.

Table 1. Adhesion severity score (Evans model)

Adhesion grade	Definition
0	no adhesions
1	filmy adhesions separate spontaneously
2	firm adhesions separated by traction
3	dense adhesions requiring sharp dissection

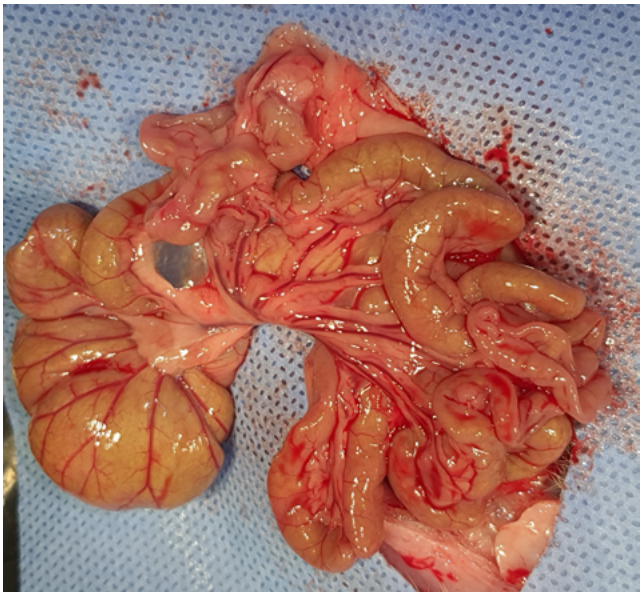

Fig. 2. Adhesion formations observed in rats following laparotomy on the 7th postoperative day. Adhesion scoring using the Evans model (grade 0: no adhesions)

The terminal ileum and cecum were dissected for histological analysis without separating the adhesions.

Histology

Tissue specimens from the terminal ileum and cecum were fixed in 10% neutral formalin and embedded in paraffin. Sections were cut from the paraffin blocks of each tissue sample using a microtome at a thickness of 4–5 µm. The specimens were then deparaffinized and stained with hematoxylin and eosin (H&E) or with Perls Prussian blue, a histochemical method for detecting hemosiderin pigments. A light microscope (Leica DM3000 LED; Leica Camera AG, Jena, Germany) was used for evaluation. The presence of adhesions and the intensity of inflammation around the terminal ileum and cecum were evaluated histopathologically (Fig. 4). These findings were observed during the microscopic evaluation of the H&E-stained sections and graded on a scale of 0 (absence of the characteristic) to 3 (intensive presence of the characteristic). Sections stained with Perls Prussian blue were evaluated for the presence of hemosiderin. The same pathologist examined all tissue sections collected for light microscopy examinations without any knowledge of the group assignments.

Statistical analyses

The data were analyzed using IBM SPSS v. 23 software (IBM Corp., Armonk, USA). The Fisher–Freeman–Halton

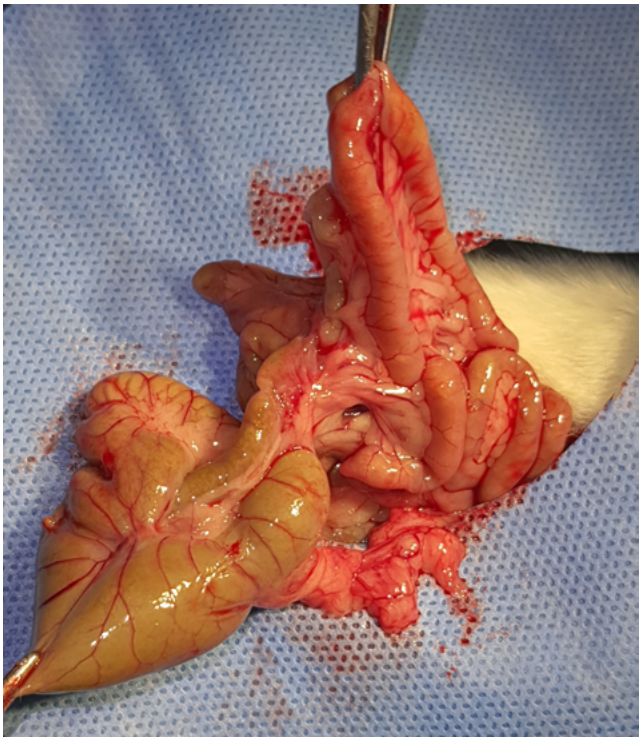

Fig. 3. Adhesion formations observed in rats following laparotomy on the 7th postoperative day. Adhesion scoring using the Evans model (grade 3: dense adhesions requiring sharp dissection)

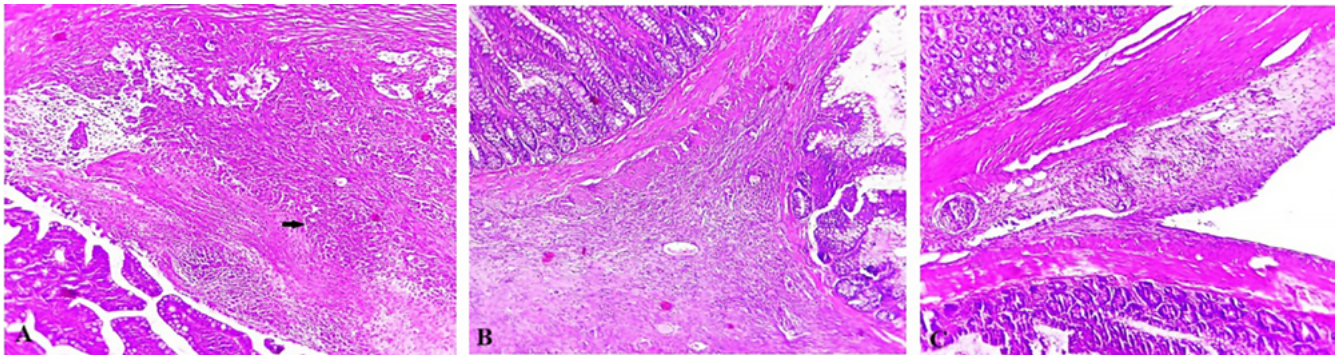

Fig. 4. Histopathological examination of adhesions and inflammation intensity around the terminal ileum-cecum. A. Photomicrograph of the control group. Serosal thickening, edema, dense inflammatory cell reaction, micro abscess focus (arrow), and granulation tissue formation in the serosal surfaces (hematoxylin & eosin (H&E) staining, ×100 magnification); B. Photomicrograph of the magnesium-treated (300 mg) group. Edema, moderate inflammatory cell reactions and granulation tissue formation on serosal surfaces (H&E, ×100 magnification); C. Photomicrograph of the magnesium-treated (500 mg) group. Edema, mild inflammatory cell reactions and granulation tissue formation on serosal surfaces (H&E, ×100 magnification)

test was used to compare categorical variables between groups since the minimum expected value was less than 5, and the data were not arranged in a 2×2 contingency table format. Additionally, multiple comparisons of proportions were examined using the Bonferroni-adjusted Z test. Categorical variables were expressed as a frequency (percentage). A p-value < 0.05 was considered statistically significant.

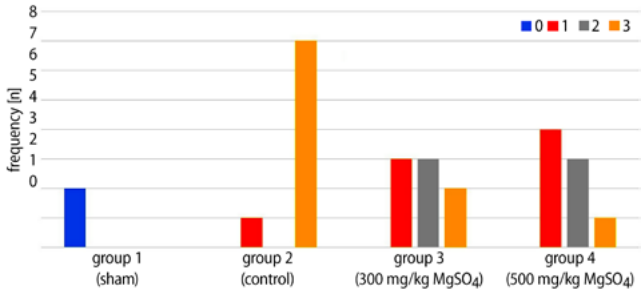

Fig. 5. Comparative analysis of adhesion severity scores across different groups using the Evans model

Results

Analysis of adhesion scores using the Evans model

Evaluation of adhesion scores according to the Evans model revealed distinct variations among the groups. In group 1, no adhesions were observed, whereas in group 2, 12.5% of cases showed filmy adhesions that separated spontaneously, and a significant majority (87.5%) of cases exhibited dense adhesions necessitating sharp dissection. In group 3, filmy adhesions that separated spontaneously and firm adhesions separable by traction were observed in 37.5% of the cases, and dense adhesions requiring sharp dissection were observed in 25% of the cases. In group 4, 50% of the cases had filmy adhesions that separated spontaneously, 37.5% had firm adhesions separable by traction, and 12.5% had dense adhesions necessitating sharp dissection. Upon evaluation, a statistically significant difference in adhesion scores across the groups was noted (p = 0.001). These results underscore the variability in adhesion characteristics and the effectiveness of the interventions in the different groups. The adhesion scores determined using the Evans model are detailed in Table 2 and illustrated in Fig. 5.

Histopathological analysis of adhesions

An analysis of adhesion scores evaluated histopathologically revealed significant differences among the groups. Histopathological findings were categorized as "none" (0), "weak"

Table 2. Comparative analysis of adhesion scores among groups based on the Evans model

Group	Adhesion score				Test statistic	p-value*
	0 n (%)	1 n (%)	2 n (%)	3 n (%)		
Group 1 (sham)	2 (100)	0 (0)	0 (0)	0 (0)	19.412	0.001
Group 2 (control)	0 (0)	1 (12.5)	0 (0)	7 (87.5)		
Group 3 (300 mg/kg $MgSO_4$)	0 (0)	3 (37.5)	3 (37.5)	2 (25)		
Group 4 (500 mg/kg $MgSO_4$)	0 (0)	4 (50)	3 (37.5)	1 (12.5)		

*Fisher–Freeman–Halton test. Adhesion severity score according to the Evans model: 0 = no adhesions, 1 = filmy adhesions separating spontaneously, 2 = firm adhesions separated by traction, 3 = dense adhesions requiring sharp dissection.

Table 3. Analysis of histopathological characteristics in tissue samples from the terminal ileum and cecum

Score	Sham				Group 2 (control, n = 8)				Group 3 (300 mg/kg $MgSO_4$, n = 8)				Group 4 (500 mg/kg $MgSO_4$, n = 8)				Test statistic	p-value*
	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3		
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)		
Mucosal inflammation	1 (50)	1 (50)	0	0	7 (87.5)	1 (12.5)	0	0	3 (37.5)	3 (37.5)	0	2 (25)	2 (25)	2 (25)	1 (12.5)	3 (37.5)	10.915	0.215
Submucosal inflammation	2 (100)	0	0	0	5 (62.5)	3 (37.5)	0	0	2 (25)	2 (25)	3 (37.5)	1 (12.5)	2 (25)	1 (12.5)	3 (37.5)	2 (25)	10.157	0.288
Serosal inflammation	2 (100)	0	0	0	0	1 (12.5)	3 (37.5)	4 (50)	2 (25)	1 (12.5)	3 (37.5)	2 (25)	1 (12.5)	3 (37.5)	2 (25)	2 (25)	9.382	0.380
Fat necrosis	2 (100)	0	0	0	8 (100)	0	0	0	4 (50)	2 (25)	2 (25)	0	4 (50)	3 (37.5)	1 (12.5)	0	7.378	0.192
Hemosiderin-laden macrophages	2 (100)	0	0	0	8 (100)	0	0	0	1 (12.5)	3 (37.5)	2 (25)	2 (25)	0	2 (25)	2 (25)	4 (50)	24.012	<0.001
Adhesion	2 (100)	0	0	0	0	8 (100)	0	0	4 (50)	4 (50)	0	0	5 (62.5)	3 (37.5)	0	0	10.216	0.016

*Fisher–Freeman–Halton test. Histopathologic findings are scored as 0 = none, 1 = weak, 2 = moderate, and 3 = intense. Adhesion is classified as 0 = absent and 1 = present.

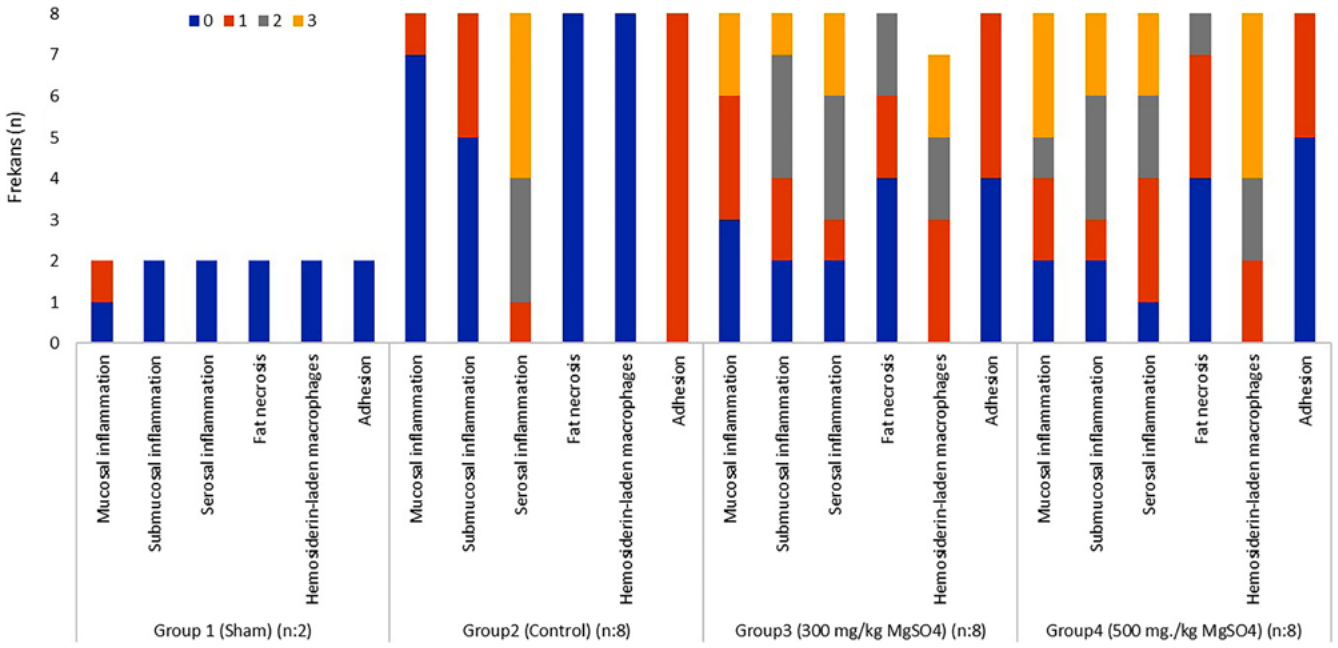

Fig. 6. Histopathological evaluation of adhesion scores in different groups. Comparison of mucosal inflammation, submucosal inflammation, fatty necrosis, macrophage infiltration, and adhesion presence

(1), "moderate" (2), or "intense" (3). Adhesions were classified as "absent" (0) or "present" (1). These histopathological findings are detailed in Table 3 and illustrated in Fig. 6.

Distribution of hemosiderin-laden macrophage scores across groups

In groups 1 and 2, hemosiderin-laden macrophages were categorized as "none" in all cases (100%), and no weak, moderate or intense instances were observed. In group 3, the distribution was found to be 12.5% "none", 37.5% "weak", 25% "moderate", and 25% "intense". In group 4, the distribution was 0% "none", 25% "weak", 25% "moderate", and 50% "intense". Based on the scores from the different groups, there were no statistically significant differences in mucosal inflammation, submucosal inflammation, serosal inflammation, or fat necrosis between the groups ($p > 0.05$). However, a statistically significant difference was noted in the scoring of hemosiderin-laden macrophages between the groups ($p < 0.001$).

Adhesion scores across groups

Significant variation was observed in the distribution of adhesion scores among the groups ($p < 0.05$). In group 1, adhesions were absent in all cases (100%). In group 2, adhesions were present in all cases (100%). In group 3, adhesions were absent in 50% of the cases and present in the remaining 50%. In group 4, adhesions were absent in 62.5% of the cases and present in 37.5% of cases.

Discussion

Our study revealed significant differences in adhesion formation among the groups ($p < 0.05$). Specifically, the Mg-treated groups (groups 3 and 4) showed significantly fewer adhesions than the control group (group 2). Our histopathological analysis revealed the detailed characteristics of these adhesions. We observed variations in the number of hemosiderin-laden macrophages among the groups. This, coupled with the differences in serosal inflammation, suggests a potential role for Mg in managing inflammation and reducing adhesion formation.

Adhesions account for 3% of all laparotomy cases and approx. 1% of general surgery admissions.[26] Various factors are implicated in adhesion formation, including rough surgical techniques, tissue drying, infections, peritoneal endometriosis, suture materials, foreign bodies, and the presence of blood or clots in the peritoneal cavity.[27] The following strategies aim to prevent adhesions by intervening in their pathophysiological mechanisms: surgical techniques, drugs, materials (such as barrier methods), and advanced technologies (such as nanoparticle and gene therapy).[28] Despite advances in modern medicine, postoperative adhesions remain an unsolved problem.[29] Adhesions can develop in response to nonsurgical or surgical injuries and are typically associated with the disruption of the balance between inflammation, fibrin formation and fibrinolysis.[27,30,31]

Local inflammation activates fibrin coagulation pathways, resulting in infiltration of inflammatory cells and fibrinogen deposition.[31,32] Fibrinogen is converted into fibrin, and if there is an imbalance between fibrin formation and fibrinolysis, adhesive bonds form.[33] As a result, abnormal intraperitoneal fibrous bands connected to the surface form abdominal adhesions.[34]

It has been observed that the levels of pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor alpha (TNF-α) increase in the peritoneal fluid during acute inflammation.[35,36] Cytokines may contribute to the remodeling of the extracellular matrix (ECM) by interacting with the fibrinolytic pathway,[37,38] promoting inflammation and coagulation, reducing fibrinolytic capacity by stimulating the release of plasminogen activator inhibitors,[39] and suppressing the production of tissue plasminogen activators.[40,41] These mechanisms suggest that the interruption of processes during the early stages of the inflammatory cascade may reduce adhesion formation.[42] The anti-inflammatory and antioxidant properties of vitamin C and vitamin E have shown potential in significantly reducing postoperative adhesions. These treatments modulate inflammatory responses and reduce oxidative stress in the affected tissues.[43] Similarly, the administration of intraperitoneal surfactant has been demonstrated to be effective in mitigating the formation of postoperative intra-abdominal adhesions, primarily by decreasing inflammation and fibrosis at the surgical site.[44]

The inhibitory effect of Mg on thrombus formation is dose-dependent and may also delay the formation of arterial blood clots by inhibiting platelet activity.[45] Calcium (Ca) ions, known as clotting factor IV, are involved in all 3 routes of clot formation,[46] and the antagonism between Ca and Mg is well known.[47] The effect of Mg on coagulation involves the displacement of Ca from the structure of procoagulant proteins. These procoagulant proteins (prothrombin, FII; blood coagulation factors FXIII, FX, FXI, FVII, FVIII, and FIX; and protein C) are Ca-dependent. However, their activity levels may decline because of excessive Mg.[45] In addition, Mg can affect coagulation through proteolysis of von Willebrand factor; thus, Mg is a natural disaggregant and anticoagulant.

The most likely mechanism of action of the anti-inflammatory effects of Mg on the arachidonic acid cascade is the direct inhibition of phospholipase.[45] According to Liu et al., hypomagnesemia induces inflammation via various signaling pathways, including the induction of cellular oxidative stress, the opening of the Ca channel, activation of the renin–angiotensin–aldosterone system and phagocytic cells, nuclear factor-kB signaling, a reduction in the levels of anti-inflammatory mediators, and the release of overactive N-methyl-D-aspartate receptors and substance P.[47] Magnesium plays a significant role in regulating intracellular pH and osmotic balance.[48] The influence of Mg on intracellular signaling pathways can modulate intracellular pH levels. This interaction has critical implications, considering the effects of intracellular pH on cellular metabolism and function. Specifically, the role of Mg in the regulation of intracellular pH is crucial for determining cellular energy metabolism and vulnerability to stress, as evidenced in mitochondrial Mg homeostasis studies.[49] The potential of Mg to reduce cell adhesion can be linked to its role in modulating the intracellular pH and relevant signaling pathways. Changes in pH can influence the conformation and function of cell adhesion molecules. Additionally, Mg may affect the signaling pathways that regulate the expression and activation of these molecules, leading to reduced adhesions.[50] This reported theoretical basis suggests a significant area for future research to fully elucidate this effect. In contrast, the effects of Mg on integrin binding affinity may affect the migration of inflammatory cells to the abraded site and their subsequent adhesion-forming function. Integrins are

cell surface receptors that play significant roles in the interaction of cells with the ECM. The activity of these receptors is crucial for processes such as cell migration and adhesion. Magnesium modulates intracellular signaling pathways and influences the binding affinity of integrins. This suggests that Mg plays a direct role in cell behavior. In particular, increases in Mg concentrations have been shown to affect the activation state of integrins, thereby altering cell migration and adhesion capacities. This interaction is supported by detailed nuclear magnetic resonance spectroscopy studies on the integrin α1 I domain, demonstrating that Mg regulates integrin-collagen recognition and binding through microsecond dynamics.[51] These interactions may have significant implications for the migration of inflammatory cells. By influencing the activity of integrins, Mg can modulate the ability of inflammatory cells to migrate to damaged tissues and form adhesions. This concept is further supported by studies on synovial stem cells, wherein Mg has been shown to enhance adhesions to collagen. This effect was inhibited by neutralizing antibodies against integrin α3 and β1, indicating the role of Mg in promoting integrin-mediated adhesion and early-phase cartilage matrix synthesis.[52]

We hypothesized that Mg would reduce adhesion development by altering thromboxane and prostaglandin synthesis via arachidonic acid metabolism, lowering vascular permeability, plasmin inhibitors, platelet aggregation, and coagulation, and modulating intracellular pH and signaling pathways. Magnesium is readily available, cost-effective and safe. Notably, this is the first study to examine the effects of Mg on intra-abdominal adhesions. To clinically evaluate adhesions, we utilized the Evans grading model and found that adhesions were noticeably reduced in the Mg groups compared to controls. Hemosiderin-laden macrophages are commonly associated with tissue repair and inflammation.[53] We found that Mg potentially accelerated the inflammation resolution phase, which may explain the observed increase in hemosiderin-laden macrophages.[54,55] Specifically, the Mg-treated groups demonstrated a significantly higher number of these macrophages than the control group ($p < 0.001$). Additionally, although not statistically significant, we noted a discernible reduction in serosal inflammation rates in the Mg-treated groups relative to the control group based on histopathological analyses. Brochhausen et al. pointed out that initial localized ischemia, followed by inflammation in the injured tissues, plays a role in the development of peritoneal adhesions.[56] There is a robust link between adhesions and serosal surface inflammation. Given the anti-inflammatory properties of Mg, the reduced inflammation observed in the Mg groups compared to the controls in the histological assessments may underscore one of the mechanisms by which Mg curbs adhesion growth. Further studies are warranted to elucidate the cellular and molecular mechanisms by which Mg inhibits adhesion development.

Limitations

This study has some limitations. First, we were uncertain about the effective intraperitoneal dose of the administered substance. Another limitation arises from the scoring of the adhesions. Although a blinded researcher performed the adhesion scoring process, the potential subjectivity and insensitivity of the observer's scoring technique may have compromised its repeatability and consistency.

Conclusions

Our findings show that Mg may be an effective agent in preventing intra-abdominal adhesions, laying the groundwork for future studies involving more detailed cellular analyses and various dosages and administration methods. Clarifying the effects of Mg on the formation of abdominal adhesions will enrich our knowledge in this area and may lead to significant changes in clinical practice.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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