

Effectiveness of atorvastatin, methylene blue, and lidocaine as chemical antiadhesion agents in preventing postoperative remote adhesions: a randomized controlled experimental study in a rat model

Young Jin Kim^{1,*}, Hyun Kang^{2,*}, Oh Haeng Lee², Seung Eun Lee³, Soon Auck Hong⁴, Suk-Won Suh^{3,†}, Yoo Shin Choi^{3,†}

¹Department of Surgery, Shihwa Medical Center, Siheung, Korea

²Department of Anesthesiology and Pain Medicine, Chung-Ang University College of Medicine, Seoul, Korea

³Department of Surgery, Chung-Ang University College of Medicine, Seoul, Korea

⁴Department of Pathology, Chung-Ang University College of Medicine, Seoul, Korea

Purpose: We investigated the antiadhesive effects of lidocaine, methylene blue, and atorvastatin, with a focus on preventing remote adhesions in a rat model of postoperative adhesions.

Methods: Models were assigned to either the control group (saline infusion only) or treatment groups (group L, lidocaine; group M, methylene blue; or group S, atorvastatin). Adhesions were induced by intestinal or abdominal wall injuries. The rats were sacrificed 2 weeks after surgery.

Results: The number of remote adhesions was markedly lower in groups L, M, and S than in the control group. The macroscopic adhesion score was substantially lower in groups L, M, and S than in the control group. Acute and chronic inflammation, as well as fibrosis scores, were also markedly lower in groups L, M, and S than in the control group. IL-1 β levels were considerably reduced in groups L, M, and S at 2 hours after surgery and remained substantially lower in group S at 48 hours. IL-6 levels were markedly reduced in groups M and S at 2 hours and in all treatment groups at 48 hours than in the control group.

Conclusion: Intraperitoneal administration of lidocaine, methylene blue, and atorvastatin effectively reduced remote adhesion formation, macroscopic and microscopic adhesion scores, and inflammatory cytokine levels in a rat adhesion model.

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Corresponding Author: Yoo Shin Choi

Department of Surgery, Chung-Ang University Hospital, 102 Heukseok-ro, Dongjak-gu, Seoul 06973, Korea

Tel: +82-2-6299-1545, Fax: +82-2-824-7869, E-mail: choiys@cau.ac.kr, ORCID: <https://orcid.org/0000-0003-3172-0329>

Co-Corresponding Author: Suk-Won Suh

Department of Surgery, Chung-Ang University Hospital, 102 Heukseok-ro, Dongjak-gu, Seoul 06973, Korea

Tel: +82-2-6299-1546, Fax: +82-2-824-7869, E-mail: bumboy1@cau.ac.kr, ORCID: <https://orcid.org/0000-0001-6111-9601>

*Young Jin Kim and Hyun Kang contributed equally to this work as co-first authors.

†Suk-Won Suh and Yoo Shin Choi contributed equally as co-corresponding authors.

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INTRODUCTION

Postoperative adhesion, a part of the healing process, involves cell proliferation, regeneration, and tissue repair [1]. However, excessive or unintended adhesions can lead to serious complications, such as intestinal obstruction, female infertility, chronic abdominal or pelvic pain, and paraplegia [2-5]. These complications often result in higher hospital readmission rates, longer patient stays, and increased healthcare costs [3-7]. Several strategies have been developed to reduce postoperative adhesions, including minimizing tissue manipulation [7], irrigating the surgical site [8], and using mechanical barriers such as films [9-11], solutions [10,12], and gels [10,12]. Chemical barriers, including anti-inflammatory agents (e.g., nonsteroidal anti-inflammatory drugs and steroids) [13], anticoagulants (e.g., heparin and warfarin) [13], fibrinolytic agents, thrombin-activated fibrinolysis inhibitors [14], and local anesthetics, have also been explored. Although a combination of mechanical and chemical barriers has shown some promise [15], no approach has been proven to be fully effective.

Most currently available antiadhesive agents act as mechanical barriers that are limited to the surgical site, which restricts their effectiveness against adhesions at distant sites, known as remote adhesions, which are often neglected despite their potential to cause significant complications. Contrastingly, chemical barriers that act on the mechanisms driving adhesion formation may have greater potential to prevent remote adhesions. Among chemical barriers, local anesthetics, methylene blue [16], and statins (such as atorvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor) [13] possess antioxidant and anti-inflammatory properties that could potentially prevent postoperative adhesions.

Therefore, we hypothesized that atorvastatin, methylene blue, and lidocaine could effectively prevent postoperative remote adhesions. In this study, we aimed to investigate the effects of these agents on postoperative remote adhesions and on gross and microscopic adhesion scores.

METHODS

Ethics statement

This randomized, controlled experimental study was conducted in accordance with the Guide for the Care and Use of Laboratory Animals [17] and adhered to the ARRIVE (Animal Research: Reporting In Vivo Experiments) guidelines [18]. The protocols and surgical procedures used for animal use were evaluated and approved by the Animal Care and Use Committee of Chung-Ang University (No. 202401030118).

Animals

The experiments were conducted at the Animal Research

Laboratory of Chung-Ang University. Adult male Sprague-Dawley rats (250–300 g; Coretec) were housed in temperature-controlled rooms (22 °C), fed a standard diet, and provided with tap water. The animals were kept on a 12-hour light/dark cycle (lights on from 8:00 a.m. to 8:00 p.m.) and acclimated for 1 week before surgery. The rats were monitored daily during the postoperative period for signs of pain and complications. Rats with health abnormalities were excluded.

Surgical technique

All surgical and anesthetic procedures were performed by a single team under semi-sterile conditions using powder-free gloves. General anesthesia was induced with 6% isoflurane in 100% oxygen in a sealed chamber until the rats were immobile. Anesthesia was maintained using 1%–2% isoflurane in 100% oxygen through a non-rebreathing mask. Cefazolin (20 mg/kg; Chong Kun Dang Pharmaceutical Co.) was administered subcutaneously before incision to prevent infection.

The surgical procedure followed previously described methods [14,15], with some modifications. Briefly, the abdominal skin was shaved and disinfected with povidone-iodine solution. Midline laparotomy was performed with a 4–5 cm incision beginning below the umbilicus. The small bowel and cecum were carefully exteriorized; adhesions were induced on the anti-mesenteric surface of the cecum and small intestine. To ensure standardized trauma, the tissue was gently abraded using an electrocautery cleaner (Johnson & Johnson) to induce superficial bleeding. This procedure was performed by an investigator and supervised by 2 observers. The abdominal wall was closed by continuous suturing using 4–0 polyglactin 910 sutures; tail tags were used for animal identification.

Randomization and study model

Rats were randomly assigned to one of the 4 groups using a randomization sequence generated using PASS 11 (NCSS, LLC.). The sequences were prepared by a statistician who was not involved in the study; the details were unknown to the investigators. Group assignments were stored in sealed envelopes and labeled only with case numbers. To maintain blinding, solutions for peritoneal instillation were prepared by a separate investigator with access to the records and placed in syringes labeled only by the case number.

The experimental groups were treated as follows: the control group (n = 30) received 5 mL of 0.9% NaCl solution; the lidocaine group (group L, n = 30) received 5 mL of lidocaine (3 mg/kg) in 0.9% NaCl solution; the methylene blue group (group M, n = 30) received 5 mL of methylene blue (30 mg/kg) in 0.9% NaCl solution; and the atorvastatin group (group S, n = 30) received 5 mL of atorvastatin (30 mg/kg) in 0.9% NaCl solution. The doses of lidocaine [19], methylene blue [20], and atorvastatin [21] were selected as described previously.

Table 1. Moreno score

Criterion	Quantification score ^{a)}
Site of adhesion	
Pelvic fat body-abdominal wall	1
Omentum-abdominal wall	2
Intestine-abdominal wall	3
Pelvic fat body or omentum-bowel	4
Intestine-intestine	5
Thickness (mm)	
<3	1
3–5	2
>5	3
Tension	
Type I (loosening without dissection)	1
Type II (loosening with blunt dissection)	2
Type III (loosening with sharp dissection)	3
Vascularization	
Not vascularized	0
Vascularized	1

^{a)}One point was assigned per adhesion.

Macroscopic assessment and adhesion scores

On postoperative day 14, the rats were euthanized by intraperitoneal injection of 100 mg/kg of 2% pentobarbital sodium; a U-shaped laparotomy was performed to assess all adhesions, sparing the initial incision site. Two blinded investigators evaluated the number of remote adhesions and macroscopic adhesion scores and reached a consensus for each rat. Macroscopic adhesions were scored using a validated adhesion scoring system that considered the number, location, thickness, tension, vascularization, and total integration of intra-abdominal adhesions (Moreno score, Table 1) [22].

Microscopic and histologic assessments

After macroscopic examination, all visceral organs with adhesions were resected. Bowel adhesion samples were fixed in 10% neutral-buffered formalin for 24 hours, embedded in paraffin, sectioned at 5 μ m, and stained with H&E using the avidin-biotin complex method. Acute and chronic inflammation and fibrosis were assessed according to the semiquantitative criteria described by Park et al. [23]. For edema and congestion, no standardized criteria have been established; therefore, these parameters were classified into none, mild, moderate, or severe on an arbitrary basis. To minimize bias, all evaluations were performed by an experienced pathologist blinded to the study purpose and group assignments.

Blood collection and immunoassay

At 2 hours, 48 hours, and 2 weeks postoperatively, 3 rats from each group were anesthetized with isoflurane, and blood samples were collected by cardiac puncture into chilled sterile

EDTA tubes (EDTA vacutainer, Becton Dickinson). Samples were centrifuged at $2,000 \times g$ for 15 minutes; plasma was separated and stored at -80°C until analysis for TNF- α , IL-1 β , and IL-6. After blood collection, rats were euthanized by intracardiac injection of pentobarbital sodium.

Serum samples from all time points were analyzed by a blinded investigator at the end of the study. TNF- α , IL-1 β , and IL-6 concentrations were measured using commercially available ELISA kits (R&D Systems).

Statistical analysis

The primary endpoint of this study was the comparison of postoperative remote adhesions between groups. Sample size was calculated based on previously reported remote adhesion values in control rats (1.64 ± 0.63) [15] using PASS 11. Assuming equal standard deviations in groups L, M, and S, and targeting reductions of 20%, 20%, and 30% for groups L, M, and S, respectively, 25 rats per group were required to achieve 80% power at a significance level of $\alpha = 0.05$ (2-tailed). To account for a 15% dropout rate, we allocated 30 rats per group and included an additional 6 rats for blood sampling at 2 and 48 hours after surgery.

Data distribution normality was assessed using the Shapiro-Wilk test. Because the data did not pass the normality test, they were analyzed using non-parametric tests. For postoperative remote adhesions, between-group comparisons were analyzed using the Kruskal-Wallis followed by the Mann-Whitney U-test with Bonferroni correction for multiple comparisons ($0.05/6 = 0.0083$).

For cytokine assays, IL-6 passed normality tests, while IL-1 β and TNF- α did not pass the Shapiro-Wilk test, but did not show marked deviation from linearity in q-q plots. Therefore, we assumed that the normal distribution assumption for parametric tests was not violated and decided to apply repeated-measures analysis of variance (ANOVA): within-subjects factor of times (at 2 hours, 48 hours, and 2 weeks) and between-subjects factor of groups (the control group and groups L, M, and S). Only intergroup effects were tested.

The Mauchly test indicated sphericity violations for IL-1 β ($\chi^2[2] = 6.319$, $P = 0.042$), IL-6 ($\chi^2[2] = 6.179$, $P = 0.046$), and TNF- α ($\chi^2[2] = 6.212$, $P = 0.047$). Therefore, a one-way Wilks' lambda multivariate ANOVA (MANOVA) was applied, with treatment groups (the control group and groups L, M, and S) as independent variables and measurements at each time point as dependent variables. For individual time-point comparisons of IL-1 β , IL-6, and TNF- α , ANOVA with the Bonferroni correction ($\alpha = 0.05/3 = 0.017$) was used. When variance homogeneity (Levene test) was violated, Welch ANOVA was applied, followed by Tamhane T2 *post-hoc* test for significant results.

Data are presented as means with standard errors in the figures and standard deviations in the tables. Associations

between remote adhesions and Moreno scores, acute and chronic inflammation, fibrosis, edema, and congestion were analyzed using the Spearman rank correlation coefficients (r). Statistical significance was set at $P < 0.05$. All analyses were performed using IBM SPSS Statistics for Windows (ver. 23.0; IBM Corp.).

RESULTS

One rat in the control group died within the first 3 postoperative days. No surgical complications were observed in the remaining rats in the control group. There were no severe postoperative adverse events, such as wound dehiscence, anorexia, or death, in groups L, M, or S. Surgical incisions healed normally; the instilled materials and sutures were fully absorbed by the time of postmortem examination.

Number of postoperative remote adhesions and macroscopic adhesion score

The control group showed the highest number of postoperative remote adhesions, which were significantly reduced in groups L (1.17 ± 0.65), M (1.23 ± 0.63), and S (0.83 ± 0.70) compared with the control group (1.72 ± 0.92) (Fig. 1A, Table 2). The number and grade of adhesions were also

significantly lower in groups L (2.37 ± 0.85 ; 3.23 ± 1.04), M (2.30 ± 0.88 ; 3.30 ± 0.95), and S (1.87 ± 1.11 ; 2.53 ± 1.33) compared with the control group (3.45 ± 1.18 ; 3.86 ± 0.69). Adhesion tension, reflecting the resistance encountered during blunt dissection, was significantly lower in groups L (2.40 ± 0.93) and S (2.23 ± 0.90) than in the control group (2.90 ± 0.31), whereas group M (2.57 ± 0.82) did not differ significantly. Finally, the total macroscopic adhesion score (Moreno score) was significantly lower in groups L (10.97 ± 2.66), M (10.92 ± 2.66), and S (9.10 ± 2.73) compared with the control group (13.21 ± 2.08), with group S scoring significantly lower than group L (Fig. 1B, Table 2).

Microscopic adhesion score

Significant differences in acute inflammation, chronic inflammation, and fibrosis were observed between the control group and group L and between groups M and S (Fig. 1C–E, Table 3). However, the edema and congestion scores did not differ significantly between the groups (Supplementary Figs. 1, 2; Table 3).

Correlations

The number of postoperative remote adhesions showed a moderate correlation with the Moreno score, chronic

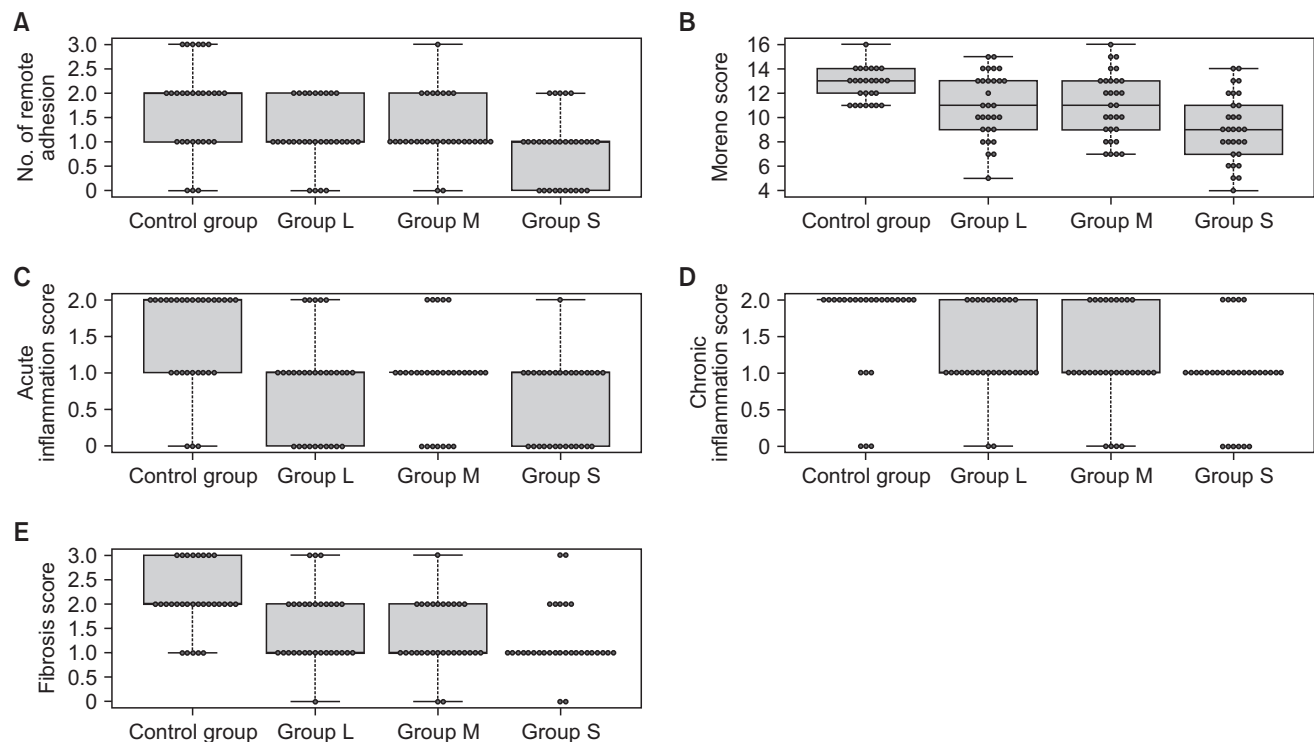


Fig. 1. Bee swarm boxplots of postoperative adhesion-related outcomes. Each boxplot displays the median and the interquartile range, and each dot represents an individual rat. (A) The number of postoperative remote adhesions. (B) The Moreno score. (C) The acute inflammation score. (D) The chronic inflammation score. (E) The fibrosis score. Bee swarm boxplot of the number of postoperative remote adhesions. Control group: received 0.9% NaCl; group L: received lidocaine (3 mg/kg); group M: received methylene blue (30 mg/kg); group S: received atorvastatin (30 mg/kg).

Table 2. Gross adhesion scores of groups

Variable	Control group (n = 29)	Group L (n = 30)	Group M (n = 30)	Group S (n = 30)	P-value
No. of remote adhesion	1.72 ± 0.92	1.17 ± 0.65*	1.23 ± 0.63*	0.83 ± 0.70* [†]	0.001
No. of adhesion	3.45 ± 1.18	2.37 ± 0.85*	2.30 ± 0.88*	1.87 ± 1.11*	<0.001
Grade	3.86 ± 0.69	3.23 ± 1.04*	3.30 ± 0.95*	2.53 ± 1.33*	<0.001
Thickness	2.55 ± 0.57	2.53 ± 0.94	2.40 ± 0.93	2.10 ± 0.88	0.222
Tension	2.90 ± 0.31	2.40 ± 0.93*	2.57 ± 0.82	2.23 ± 0.90*	0.003
Vascularization	0.45 ± 0.51	0.27 ± 0.45	0.33 ± 0.48	0.27 ± 0.45	0.877
Moreno score	13.21 ± 2.08	10.97 ± 2.66*	10.92 ± 2.66*	9.10 ± 2.73* [†]	<0.001

Values are presented as mean ± standard deviation.

Control group: received 0.9% NaCl; group L: received lidocaine (3 mg/kg); group M: received methylene blue (30 mg/kg); group S: received atorvastatin (30 mg/kg).

Kruskal-Wallis followed by the Mann-Whitney U-test with Bonferroni correction was used because of abnormal distribution.

*P < 0.05 compared with control group, [†]P < 0.05 compared with group L.

Table 3. Microscopic adhesion score

Variable	Control group (n = 29)	Group L (n = 30)	Group M (n = 30)	Group S (n = 30)	P-value
Acute inflammation	1.48 ± 0.69	0.83 ± 0.70*	0.93 ± 0.64*	0.60 ± 0.56*	<0.001
Chronic inflammation	1.86 ± 0.83	1.27 ± 0.58*	1.17 ± 0.65*	0.97 ± 0.61*	<0.001
Fibrosis	2.10 ± 0.67	1.53 ± 0.73*	1.43 ± 0.82*	1.23 ± 0.68*	<0.001
Edema	0.34 ± 0.77	0.30 ± 0.60	0.30 ± 0.53	0.13 ± 0.43	0.449
Congestion	0.79 ± 0.86	1.13 ± 0.73	1.13 ± 0.68	0.87 ± 0.73	0.134

Values are presented as mean ± standard deviation.

Control group: received 0.9% NaCl; group L: received lidocaine (3 mg/kg); group M: received methylene blue (30 mg/kg); group S: received atorvastatin (30 mg/kg).

Kruskal-Wallis followed by the Mann-Whitney U-test with Bonferroni correction was used because of abnormal distribution.

*P < 0.05 compared with the control group.

inflammation, and fibrosis grade ($\rho = 0.191$, $P = 0.038$; $\rho = 0.216$, $P = 0.018$; and $\rho = 0.282$, $P = 0.002$, respectively) (Supplementary Figs. 3–5). No significant correlation was found between postoperative remote adhesions and acute inflammation, edema, or congestion ($\rho = 0.168$, $P = 0.069$; $\rho = 0.082$, $P = 0.375$; and $\rho = 0.057$, $P = 0.541$, respectively) (Supplementary Figs. 6–8).

The Moreno score was correlated fairly well with acute inflammation, chronic inflammation, and fibrosis grade ($\rho = 0.209$, $P = 0.022$; $\rho = 0.221$, $P = 0.016$; and $\rho = 0.319$, $P < 0.001$, respectively) (Supplementary Figs. 9–11). However, the Moreno scores were not significantly correlated with edema and congestion ($\rho = -0.023$, $P = 0.803$; $\rho = -0.094$, $P = 0.308$, respectively) (Supplementary Figs. 12, 13).

Cytokine assays

Fig. 2A illustrates IL-1 β level changes. MANOVA analysis results indicated a statistically significant difference among the groups ($F[9, 14.753] = 2.868$, $P = 0.035$; Wilks' lambda = 0.085, partial $\eta^2 = 0.560$). Compared to the control group, IL-1 β levels were significantly lower in groups L, M, and S at 2 hours after surgery, with group S also showing significantly decreased IL-1 β levels at 48 hours after surgery.

Fig. 2B shows IL-6 level changes. MANOVA results indicated a statistically significant difference among the groups ($F[9, 14.753] = 2.616$, $P = 0.049$; Wilks' lambda = 0.098, partial $\eta^2 = 0.539$). Compared to the control group, IL-6 levels were significantly lower in groups M and S at 2 hours after surgery and in groups L, M, and S at 48 hours after surgery.

There were no significant differences in TNF- α levels among the groups ($F[9, 14.753] = 1.594$, $P = 0.205$; Wilks' lambda = 0.191, partial $\eta^2 = 0.424$) (Fig. 2C).

DISCUSSION

In this preclinical study, we found that the direct administration of lidocaine, methylene blue, and atorvastatin into the abdominal cavity reduced postoperative adhesions. Groups treated with these agents (groups L, M, and S) had fewer remote adhesions and lower macroscopic adhesion scores than the control group. Histological analysis confirmed these results, showing reduced acute and chronic inflammation, and fibrosis. Cytokine tests revealed lower levels of the inflammatory markers IL-1 β and IL-6 in the treated groups.

Postoperative adhesions are a common, serious surgical complication. A systematic review indicated that small bowel

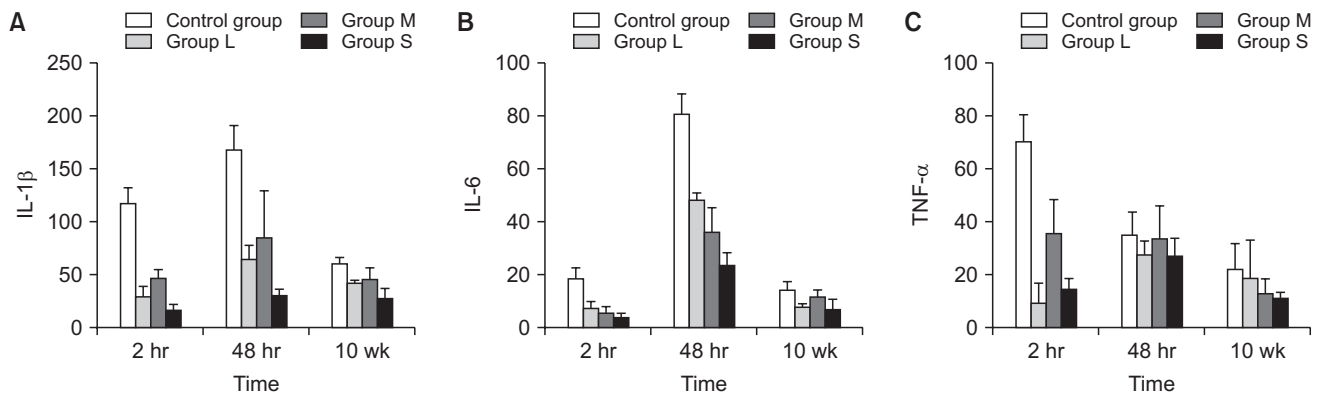


Fig. 2. Plasma concentrations of inflammatory cytokines. (A) IL-1 β . (B) IL-6. (C) TNF- α . Values are presented as mean $\pm$ standard deviation. Control group: received 0.9% NaCl; group L: received lidocaine (3 mg/kg); group M: received methylene blue (30 mg/kg); group S: received atorvastatin (30 mg/kg). * $P < 0.05$ compared with the control group.

obstruction occurs in approximately 9% of cases, with adhesions causing approximately 2.4% of these cases and requiring reoperation in a similar percentage of patients. Notably, adhesions are the primary cause of postoperative small bowel obstruction, accounting for 56% of cases [5]. Adhesion-related surgeries such as adhesiolysis can lead to various complications, including bleeding, accidental bowel injury, damage to peritoneal organs [24], and the need to switch from laparoscopic to open surgery, in turn increasing morbidity, mortality [25,26], and healthcare costs and burden [7]. Adhesion formation in areas away from the surgical site (remote adhesions) is another significant postoperative complication; however, it has not been well-researched despite its potential for severe consequences.

Various strategies developed to address these issues are mainly categorized into 2 types: physical and chemical barriers. Physical barriers are designed to cover the surgical site and reduce the contact between the injured and surrounding tissues. Chemical barriers can inhibit the biological processes responsible for adhesion formation [10]. Currently available antiadhesive agents mostly act as physical barriers, limiting their effects at the surgical site. This restricts their ability to prevent adhesions in areas away from the surgery, or "remote adhesions," which can also lead to complications. Although physical barriers effectively minimize adhesions at the surgical sites, they have inherent limitations in preventing remote adhesions. Chemical barriers that target the biological pathways of adhesion may offer a broader, more effective solution in preventing remote adhesions. Among these, local anesthetics, methylene blue [16], and statins [13] have been widely studied in both preclinical and clinical settings, given their potential to reduce postoperative adhesions.

Local anesthetics, by reducing ILs (IL-1 and IL-6) and TNF- α , help minimize inflammation and postoperative adhesion formation. They also provide pain relief and aid patient comfort and mobility, which can indirectly reduce the

immune response. Additionally, local anesthetics activate the fibrinolytic system, lower the levels of factor VIII, plasminogen, and alpha-2-antiplasmin, and inhibit platelet aggregation [27]. Methylene blue, a widely used medical dye, has antioxidant properties that reduce oxygen radical production and can prevent adhesions [28]. It also has antibacterial effects and can suppress inflammatory markers, such as IL-1, IL-6, and TNF- α [29]. Statins, commonly prescribed to lower cholesterol, show promise for adhesion prevention owing to their antioxidant, anti-inflammatory, and profibrinolytic effects [30]. Statins modulate fibrinolysis in both normal and inflamed tissues, potentially preventing adhesions [31]. Among the 3 agents, atorvastatin demonstrated superior antiadhesion effects. In addition to their anti-inflammatory properties, statins are known to enhance fibrinolytic activity, thereby promoting the absorption of intra-abdominal clots and fibrin. This dual action may explain why statins exhibited more pronounced efficacy compared with lidocaine or methylene blue.

Surgical trauma triggers an inflammatory response, in which macrophages and mesothelial cells produce tissue factors that activate the coagulation cascade, leading to a fibrin-rich inflammatory exudate [32]. While normal fibrinolysis can reverse this process, fibrinolysis is often inhibited in ischemic or inflamed tissues, resulting in inflammatory cells and fibroblasts infiltrating the fibrin bands, thereby forming adhesions. Therefore, the antioxidant, anti-inflammatory, and profibrinolytic properties of local anesthetics, methylene blue, and statins could help prevent postoperative adhesions.

We showed that lidocaine, methylene blue, and atorvastatin reduced acute and chronic inflammation in the treatment groups compared with that in the control group. This reduction in inflammation, confirmed by lower IL-1 β and IL-6 serum levels in the treatment groups, suggests that these agents, when applied at the surgical site, can mitigate inflammatory responses and reduce tissue damage. In contrast, TNF levels

showed only a decreasing tendency in the treatment groups, but the difference did not reach statistical significance. This may be explained by the relatively small sample size, which could have limited the statistical power to detect subtle differences, as well as the inherent variability of TNF responses. Furthermore, although our study focused on comparing the individual effects of lidocaine, methylene blue, and atorvastatin, we did not evaluate their combined use. Future investigations exploring potential synergistic effects of combination regimens may provide deeper insights into optimizing adhesion prevention strategies.

Our study has several limitations. First, we did not explore the effects of different doses of lidocaine, methylene blue, or atorvastatin. The doses were selected based on previous studies that demonstrated their efficacy. However, these may not represent the optimal doses for adhesion prevention because different doses can produce variable outcomes. Second, the rat model used in our study may not fully represent all cases of postoperative adhesions. For broader clinical relevance, additional research is needed in other models of abdominal or pelvic surgery where postoperative adhesion prevention is crucial. Third, adhesion formation is largely completed within weeks after surgery, but our observation period was limited to 2 weeks and thus did not assess long-term adhesion outcomes. Furthermore, our study did not account for differences between laparoscopic and open surgical approaches, which may influence adhesion development. These factors should be considered when extrapolating our findings to human clinical practice.

In conclusion, the intraperitoneal application of lidocaine, methylene blue, and atorvastatin effectively reduced the number of remote adhesions and the macroscopic and

microscopic adhesion scores. Their antiadhesive properties may be associated with their anti-inflammatory effects.

SUPPLEMENTARY MATERIALS

Supplementary Figs. 1–13 can be found via <https://doi.org/10.4174/astr.2026.110.1.56>.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

ORCID iD

Young Jin Kim: <https://orcid.org/0000-0002-3878-3085>

Hyun Kang: <https://orcid.org/0000-0003-2844-5880>

Oh Haeng Lee: <https://orcid.org/0000-0002-2117-1437>

Seung Eun Lee: <https://orcid.org/0000-0003-1830-9666>

Soon Auck Hong: <https://orcid.org/0000-0002-7902-4608>

Suk-Won Suh: <https://orcid.org/0000-0001-6111-9601>

Yoo Shin Choi: <https://orcid.org/0000-0003-3172-0329>

Author Contribution

Conceptualization, Data curation, Methodology, Resources: SWS, YSC, HK, OHL

Formal analysis: SWS, YJK, YSC, SEL, SAH

Writing – Original Draft: All authors

Writing – Review & Editing: All authors

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