

Comparison of the effects of Enalapril and meloxicam in preventing postoperative intra-abdominal adhesions in rabbits based on oxidative stress and inflammation

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Abstract

Postoperative adhesions cause pain and organ dysfunction, with inflammation and angiogenesis playing crucial roles in their pathophysiology. Inhibitors of the renin-angiotensin system may reduce adhesion formation by mitigating inflammation and free radical production. To investigate the anti-inflammatory and antioxidant effects of Enalapril and meloxicam in preventing postoperative adhesion formation following abdominal surgery in a rabbit model. Intra-abdominal adhesions were induced in twenty-four New Zealand White rabbits and then treated in four groups using distilled water, Enalapril, meloxicam, and enalapril + meloxicam (21 days). On days 14 and 21, pathological samples and markers of oxidative and inflammatory stress were studied.

Results: Enalapril caused a slight decrease in the adhesion index, but the combination of Enalapril and meloxicam significantly reduced it. Similarly, in reducing inflammatory factors (TNF- α and IL-1 β), increasing oxidative stress enzymes (SOD, CAT, GPx), and reducing MDA, meloxicam was more effective than Enalapril. Furthermore, in the group receiving Enalapril and meloxicam, the inhibition of inflammation and oxidative stress was significantly greater than that observed in the control group. The combination of Enalapril and meloxicam was significantly more effective than Enalapril alone in reducing the adhesion index.

Keywords: Abdominal adhesion; Enalapril; Inflammation; Meloxicam; Oxidative stress; Rabbit.

1. Introduction

Postoperative adhesions develop in 50% to 97% of patients after abdominal surgery [1, 2]. Adhesions are abnormal fibrous connections that may contain vascular channels and join tissue surfaces at abnormal locations [3]. They frequently cause postoperative ileus, chronic abdominopelvic pain, infertility, and longer operation times, and increase the risk of intraoperative complications [4]. The compounds and methods used to prevent adhesions should not inhibit wound healing and

should be effective in the presence of blood or other body fluids. They should also have anti-inflammatory properties, be free of immunogenic agents, be biodegradable, remain in place after use, be easy to apply, and have an immediate effect [5]. The use of physical barriers, modification of surgical technique, and administration of medications such as glucocorticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), fibrinolytic agents, anticoagulants, growth factor inhibitors, and antibiotics have been

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recommended to prevent postoperative adhesions. However, their definitive efficacy has not been confirmed yet [6, 7]. Several studies have demonstrated that free radicals contribute to the development of adhesions following abdominal surgery [2, 4]. Surgery increases the activity of free radicals, such as superoxide anions, and leads to the production of Malondialdehyde (MDA) [4].

On the other hand, inflammation and angiogenesis also contribute to the pathophysiology of peritoneal adhesions. Increased secretion of tumour necrosis factor alpha (TNF- α), interleukin (IL)-1 β , IL-6, platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF) has been observed at the site of adhesion formation [8]. The renin-angiotensin system (RAS), a key regulator of blood pressure, has been demonstrated in recent studies to play a significant role in promoting fibrosis, proliferation, inflammation, and oxidative stress [9]. Evidence shows that angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and direct renin inhibitors (DRIs) can prevent postoperative adhesions [8]. Enalapril inhibited wear Ti particle-induced "inflammatory osteolysis" in a mouse model by inhibiting the expression of the inflammatory cytokines vascular endothelial growth factor and TNF- α [10]. ACEIs can also reduce fibrosis and tendon adhesion in mice. The effects of ACEIs are due to their inhibition of angiotensin II and their antifibrotic effects [11]. Since damage to the mesothelial cell layer results in elevated levels of leukotriene B4 and prostaglandin E2 (PGE2) in peritoneal fluid [12], several nonsteroidal anti-inflammatory drugs (NSAIDs) have been used in many clinical and animal studies to minimise or prevent adhesion formation after surgery [13]. Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce inflammation by inhibiting the production of prostaglandins. Meloxicam is an NSAID that inhibits cyclooxygenase-2 (COX-2) more than COX-1. COX-2 is induced by inflammatory stimuli under pathophysiological conditions [14]. Therefore, it seems that NSAIDs may be effective in reducing or preventing postoperative adhesions. This study aimed to investigate the effects of Enalapril, an ACE inhibitor, and meloxicam, an NSAID, alone and in combination, on postoperative adhesions in rabbits.

2. Materials and Methods

2.1. Drugs

Enalapril was purchased from Sigma-Aldrich (United States of America); Meloxicam 2% vial was purchased from Zarrin Pakhsh (Iran); enrofloxacin 10% was purchased from Rooyan Darou (Iran); ketamine 10% was purchased from Bremer Pharma (Germany); xylazine 2% was purchased from Rooyan Darou (Iran).

2.2. Animals

Ethical approval for the study was obtained from the Laboratory Animal Ethics Committee of Islamic Azad University, Iran (Ethical approval ID: IR.IAU.SHK.REC.1403.034). Twenty-four New Zealand White rabbits (2.5–3 kg) aged 6–8 weeks were used. The animals were housed under standard conditions (environmental temperature of 20 ± 3 °C, light/dark cycle of 12 h/12 h) for 1 week prior to the experiment, in individual cages with adequate bedding and access to standard food and tap water.

2.3. Adhesion induction method

Rabbits were anaesthetised with ketamine (35 mg/kg) and xylazine (5 mg/kg). All the surgery was performed under aseptic conditions. The abdominal skin was shaved and disinfected with 10% povidone-iodine solution. Then, a 6 cm long incision was made in the skin and linea alba. The descending colon was located, and its serous surface (in the non-vascular area) was scratched by rubbing dry sterile gauze 100 times (according to the standard method) until petechiae appeared on its serous surface. Then, 10 parallel incisions of 2–3 cm in length were made with a scalpel on the peritoneal surface of the left abdominal wall adjacent to the descending colon area. Then, the abdominal muscles were sutured with Vicryl suture with a simple continuous suture, and the skin was sutured with nylon suture [15]. A single dose of 5% enrofloxacin at 15 mg/kg was administered to all rabbits to prevent wound infection. The rabbits were kept at appropriate temperature conditions until they regained consciousness. External sutures were removed after ten days. The surgical site was disinfected with oxytetracycline spray for 7 days. Rabbits were randomly assigned to 4 groups. Group 1: 1 mL normal saline IP

(control). Group 2: enalapril (5 mg/kg IP). Group 3: meloxicam (0.6 mg/kg IP). Group 4: meloxicam and enalapril (at the same doses) IP. Drugs were injected daily for 21 days.

2.4. Adhesion evaluation

To examine the adhesion process, 3 rabbits from each group were sampled on day 14 and 3 on day 21 as follows: First, the rabbits were anesthetised with a ketamine-xylazine combination, then the abdomen was opened at the midline, and a blinded observer scored the adhesion. Adhesions were assessed macroscopically according to the adhesion scoring system defined by Nair [16] (Table 1).

Table 1. Nair scoring system [16].

0	No adhesion
1	A single adhesion between an organ and the abdominal wall or two organs
2	adhesions between organs or an organ and the abdominal wall.
3	More than two adhesions between organs or extensive intestinal adhesions without adhesion to the abdominal wall
4	Generalized adhesions between organs and the abdominal wall or extensive adhesions between all organs

2.5. Sampling

Small pieces of peritoneal tissue of the abdominal wall and the tissues and organs attached to it were separated for the following tests. The small pieces of the specimen were stored at -80 °C until assessment of oxidative stress factors and the expression of inflammatory genes.

2.6. Histopathological evaluation

One part of the sample was first placed in a 10% formalin solution for microscopic examination. Then, histopathological examinations were performed by a pathologist unaware of the groupings using a light microscope.

2.7. Measurement of oxidative stress factors

The indices of oxidative stress, including superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and MDA, were measured in the

experimental groups using colourimetric kits according to the manufacturer's protocol. The kits SOD, CAT, GPx, and MDA used in this study were purchased from Kiazist Company (Iran).

2.8. Measurement of inflammatory factors by Real-time PCR

Real-time PCR was used to assess inflammation by measuring the expression of the relevant inflammatory genes IL1- β and TNF- α . First, 100 mg of the tissue sample was homogenised, and total RNA was extracted using a commercial kit (BIOZOL, Bioer, China) according to the instructions. The quality of the extracted RNA was assessed using agarose gel electrophoresis. After that, RNA quantity was determined using a Nanodrop 2000 spectrophotometer (Thermo, USA) by measuring absorbance at 260 nm and 280 nm. To eliminate the possibility of DNA in the extracted RNA sample, a DNase I kit (Gen Sina, Iran) was used. A cDNA synthesis kit (Yekta Tajhiz, Iran) was used to convert RNA to cDNA. After cDNA formation, in the presence of specific primers, the expression of the target genes was measured by Real-Time PCR. The primer list is given in Table 2. The GAPDH gene was used as an internal control to normalise and control mRNA expression. The RT-qPCR process was performed in 45 cycles. The final reaction volume was 20 μ L, containing 12 μ L of master mix, 3 μ L of cDNA, 1 μ L of primers F and R, and 4 μ L of sterile distilled water. The qPCR steps included denaturation at 95°C for 15 seconds, primer annealing at 60°C for 20 s, and extension at 72°C for 25 s. All Real-Time PCR amplifications were performed in triplicate. The $2^{-\Delta\Delta CT}$ method was used for statistical analysis [17].

Table 2. The sequence of primers used in this study is listed in the table below.

Gene name	Primer sequence 5' to 3'
TNF- α -F	CTGGCGTGTTCATCCGTTC
TNF- α -R	GGCTCTGAGGAGTAGACGATAA
IL1- β -F	CAACAAAAATGCCTCGTGCTG
IL1- β -R	TCGTTGCTTGTCTCTCCTTGTA
GAPDH-F	TTGGCTACAGCAACAGG
GAPDH-R	GGGGAGATTCAAGTGTGG

2.9. Statistical analysis

The results are analysed using SPSS statistical software, descriptive statistics (tables and graphs), and inferential statistics (one-way analysis of variance [ANOVA] and Tukey post hoc test), and $P < 0.05$ is considered significant.

3. Results and Discussion

3.1. adhesion index

Figure 1 shows the adhesion bands. In **Figure 1a**, grade 4 adhesion is seen between the cecum and the abdominal wall. **Figure 1b** shows grade 3 adhesion. **Figure 1c**

shows the formation of thin bands and grade 2 adhesion. **Figure 1d** shows the absence of adhesion bands. The highest and most severe adhesion was observed in the control group, and the lowest in the Enalapril + meloxicam group. **Figure 2** compares the adhesion index between different groups on days 14 and 21. The results show that administration of Enalapril or meloxicam alone did not significantly prevent adhesion formation, but the combination of Enalapril + meloxicam significantly reduced the occurrence of adhesion. There was no significant difference in the adhesion index between days 14 and 21.

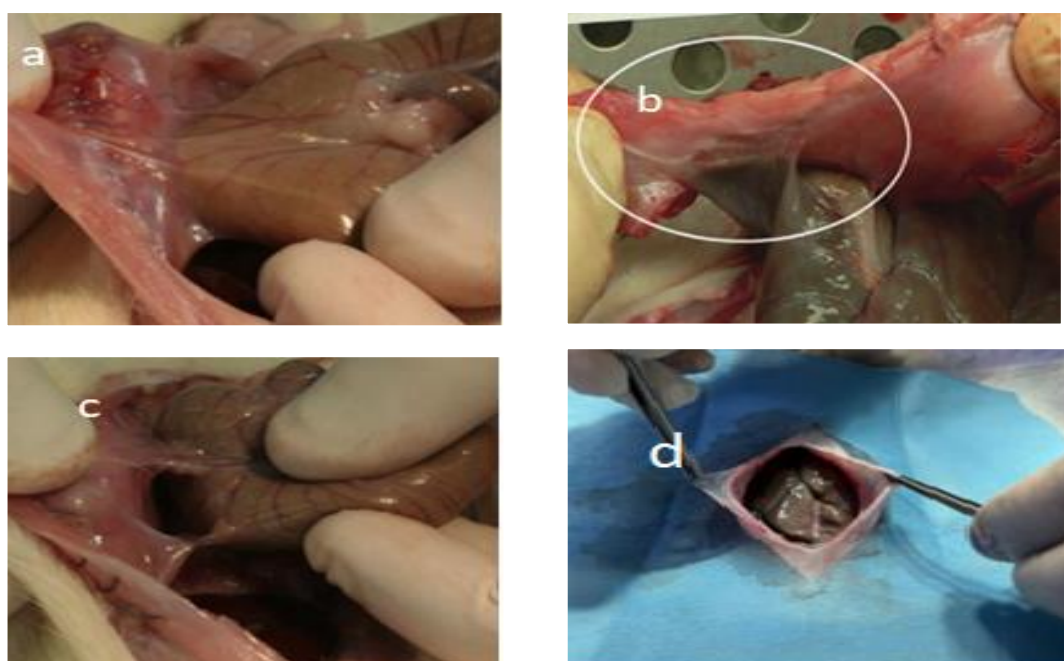


Figure 1. Images of adhesion severity in rabbits on day 21: a) Severe adhesion between the cecum and the inner abdominal wall in the control group. b) Relatively thin adhesion bands in the enalapril group. c) Two thin adhesion bands in the meloxicam group. d) No adhesion formation in the enalapril + meloxicam group..

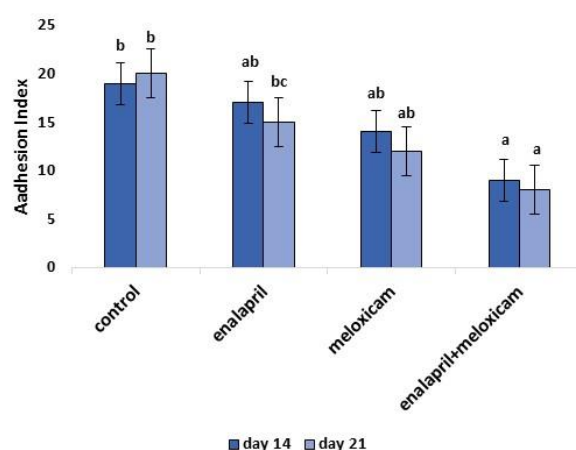


Figure 2. Comparison of intra-abdominal adhesion index between treatment groups and between days 14 and 21 in rabbits. Based on Tukey's HSD test, groups sharing at least one common letter are not significantly different from each other ($p > 0.05$).

3.2. Histopathologic results

Tissue changes were assessed in two aspects: fibrosis formation (indicated by collagen deposition) and the degree of inflammation and bleeding. The control group exhibited the highest levels of fibrosis and collagen formation on days 14 and 21, whereas the enalapril + meloxicam group showed the lowest levels of fibrosis (Table 3).

Histopathological images are shown in Figure 3. Fibrosis and inflammation were observed in the control group on day 14, with a slight increase in fibrosis and a

decrease in inflammation on day 21 (Figures 3A and 3B). Figures 3. C, D (enalapril group) show fibrosis and inflammation that are not significantly different between days 14 and 21, although the severity of inflammation and fibrosis is less than in the control group. Figures 3E and 3F (meloxicam group) are equivalent to the enalapril group. With the coadministration of Enalapril and meloxicam (Figures 3G and 3H), a significant reduction in fibrosis is observed compared with the control group, while no significant difference in inflammation is observed.

Table 3. The histopathological observations in different treatment groups.

groups	Day 14		Day 21	
	Fibrosis	Inflammation	Fibrosis	Inflammation
Control	++	+++	++++	+
Enalapril	++	++	+++	+
Meloxicam	++	+	++	+
Enalapril+Meloxicam	+	-	+	-

(-) No damage, (+) Low and light damage, (++) Medium damage, (+++) High damage

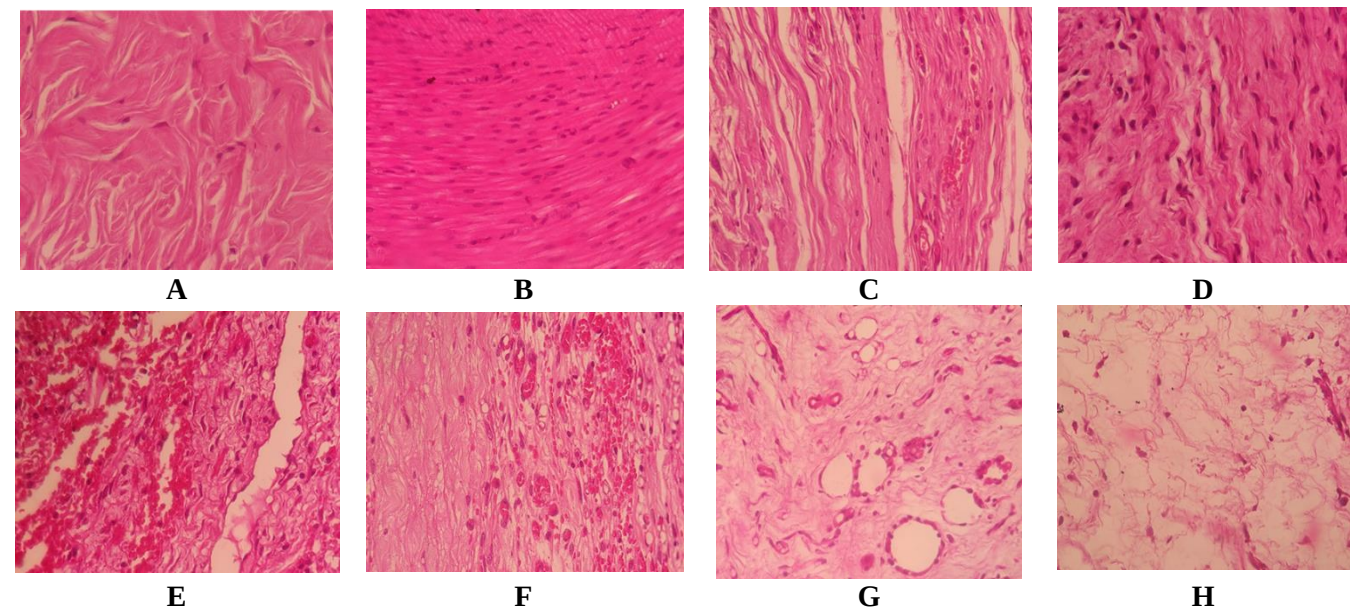


Figure3. Histopathological changes after induction of intra-abdominal adhesions in rabbits: A - Formation of very dense connective tissue and presence of fibrocytes and inflammation on day 14 in the control group. B - Increased fibrosis and decreased inflammation on day 21 in the control group. C - Enalapril group on day 14, D - Enalapril group on day 21: Dense fibrous tissue and fibrocytes were observed, with no significant difference between days 14 and 21. E - Meloxicam group on day 14, F - Meloxicam group on day 21, with moderate hemorrhage and fibrosis without a significant difference between days 14 and 21. G - Enalapril + Meloxicam group on day 14, H - Enalapril + Meloxicam group on day 21: Fine connective tissue and a significant decrease in fibrosis compared with the control group.

3.3. Results of the expression of proinflammatory genes

As shown in **Figure 4**, IL-1 β gene expression increased in the control group. Enalapril significantly reduced this increase on days 14 and 21. On day 14, IL-1 β expression in the meloxicam group was significantly lower than in the control group ($P < 0.0009$); by day 21, it was also significantly lower than in the enalapril group. The meloxicam + enalapril group showed a significant decrease in IL-1 β expression compared to the control, Enalapril, and meloxicam groups ($P < 0.0001$). Within this combination group, the change in expression between day 14 and day 21 was not significant. TNF- α gene expression increased following adhesion induction. Enalapril significantly reduced this expression by day 21 ($p < 0.0001$). Meloxicam produced a more substantial effect, significantly reducing TNF- α levels on both days 14 and 21 compared to the control and enalapril groups ($p < 0.0001$), with a significant change also observed between these two time points. The combination therapy (Enalapril + meloxicam) was the most effective. On day 14, it significantly decreased TNF- α expression compared to the control ($p < 0.0001$), Enalapril ($p < 0.0001$), and meloxicam ($p = 0.0055$) groups. This significant reduction compared to the control and enalapril groups was maintained on day 21 ($p < 0.0001$).

Within the combination group, the change from day 14 to day 21 was not statistically significant ($p = 0.026$).

3.4. Evaluation of antioxidant markers

Figure 5 presents the levels of oxidative stress markers, including MDA, SOD, CAT, and GPx, in the different experimental groups on day 21. Following the induction of intra-abdominal adhesions and administration of the treatments, MDA levels, a marker of lipid peroxidation, were reduced compared with the control group. The greatest reduction was observed in the enalapril + meloxicam group; however, the difference was not statistically significant (**Figure 5A**).

The induction of adhesions was associated with increased oxidative stress and a concomitant decrease in antioxidant enzyme activities. Treatment with either Enalapril or meloxicam alone increased the activities of SOD, CAT, and GPx compared with the control group. Notably, the combined administration of Enalapril and meloxicam resulted in a greater increase in the activities of these antioxidant enzymes, with the differences reaching statistical significance compared with the control group (**Figure 5B–D**).

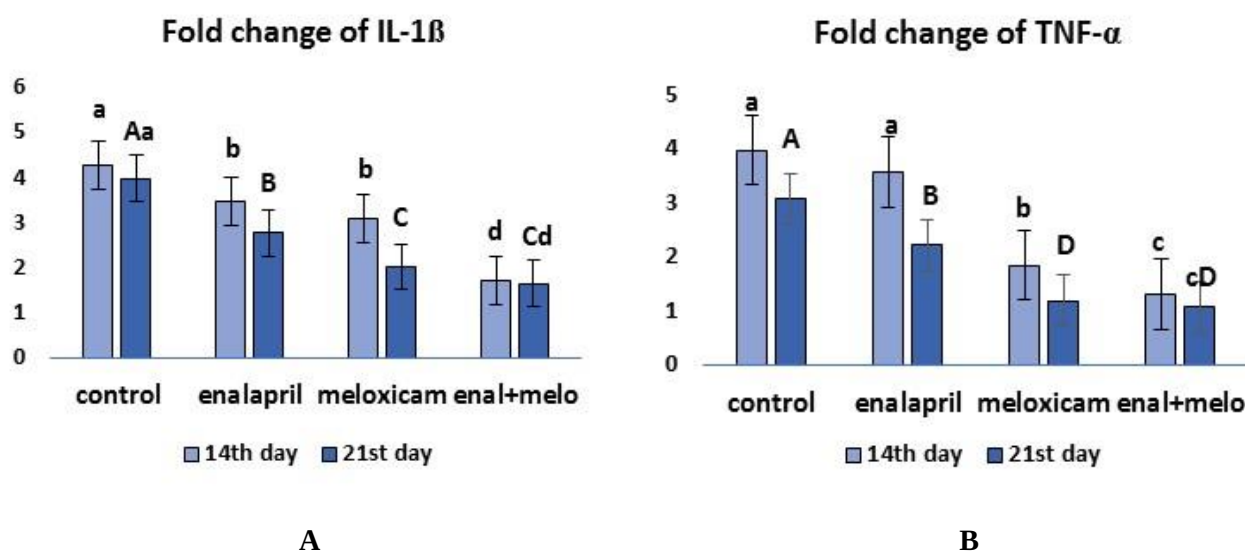


Figure 4. Comparison of fold change of IL-1 β and TNF- α in treatment groups between day 14 and day 21 in rabbits. Lowercase Latin letters indicate statistically significant differences between groups on day 14, and uppercase Latin letters indicate statistically significant differences between groups on day 21 ($p < 0.05$).

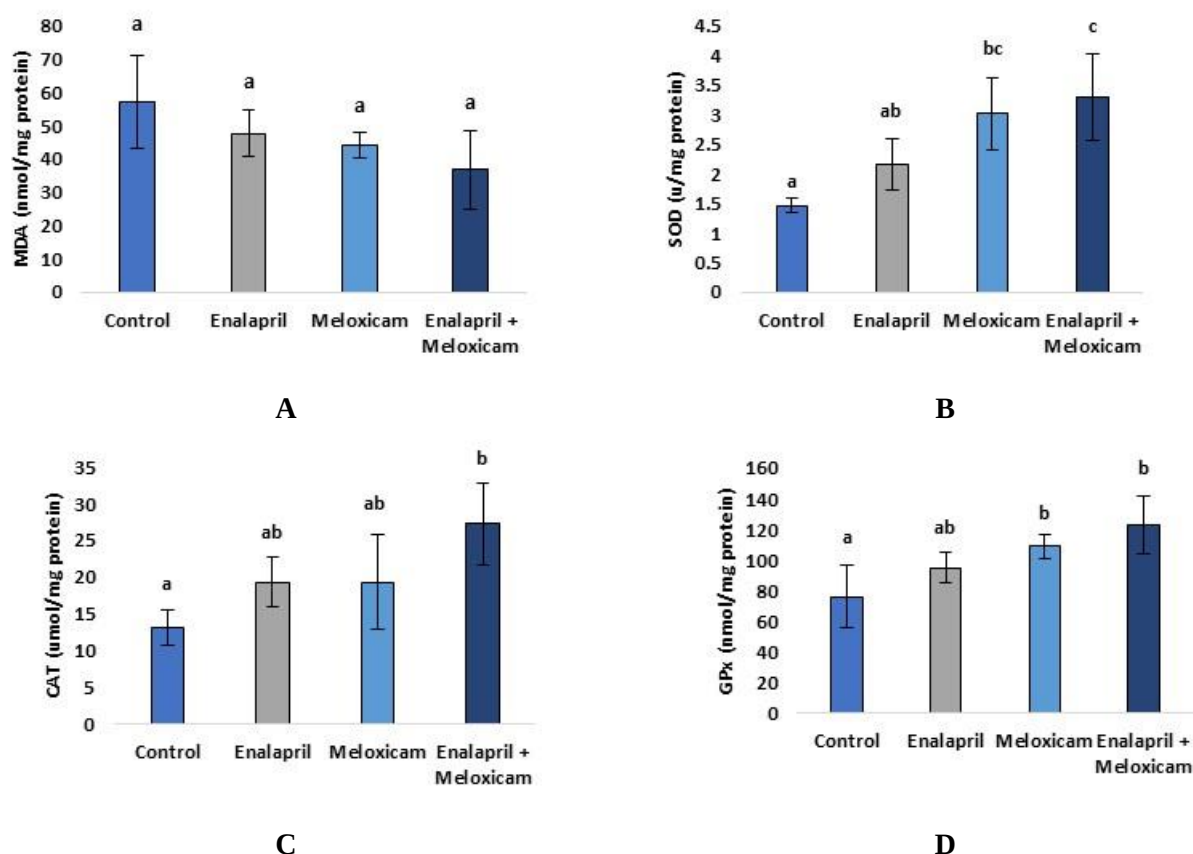


Figure 5. Effects of enalapril and meloxicam on lipid peroxidation, as indicated by MDA (A), and antioxidant activity of SOD (B), CAT (C), and GPx (D) on induced intra-abdominal adhesion in rabbits on day 21. Similar lowercase Latin letters indicate no statistically significant difference ($p > 0.05$).

3.5. Discussion

The mechanism of abdominal adhesion is associated with an imbalance in the fibrinolytic system, inflammatory response, oxidative stress, and the processes of proliferation and angiogenesis [18]. Therefore, any agent that can reduce inflammatory responses and oxidative stress, stimulate fibrinolysis, or prevent fibroblast proliferation and collagen production at the injured site can prevent intra-abdominal adhesion formation. The present study investigated the Effect of Enalapril and meloxicam on inhibiting intra-abdominal adhesions after surgery in rabbits. The results showed that these drugs alone partially reduced tissue fibrosis, inflammation, and bleeding, as well as oxidative stress and proinflammatory cytokines, but had no significant effect on adhesion rates. However, the coadministration of Enalapril and meloxicam reduced the occurrence and severity of adhesions.

In a study, the properties of Enalapril (0.75 mg/day) on wound healing were evaluated in rabbits. Enalapril reduced the inflammation of hypertrophic scars by reducing collagen production [19]. In another study, the effect of lisinopril, an angiotensin-converting enzyme inhibitor, on intra-abdominal adhesion formation was investigated, and the results showed that adhesion severity was significantly lower in the ACE inhibitor group [20]. Telmisartan and Enalapril reduced the macroscopic score of adhesion, collagen deposition, and fibrosis in tendon tissues after surgery in rabbits. This effect has been attributed to the anti-inflammatory and antioxidant properties of angiotensin pathway inhibitors [21]. Nonsteroidal anti-inflammatory drugs are used to control pain after surgeries such as laparotomy and thoracotomy [22]. These drugs have been shown to prevent intra-abdominal adhesions. In a 2010 study by Bourque et al., the effects of meloxicam and buprenorphine on physiological indices after laparotomy

in rats were investigated, and the superiority of meloxicam over buprenorphine was demonstrated [23]. Comparing the effects of meloxicam and dexketoprofen on the inhibition of postoperative adhesions in rat uterine horn surgery, although meloxicam did not affect clinical adhesion formation, it significantly reduced histological scores compared with the control group. Therefore, meloxicam may be suitable for reducing postoperative intra-abdominal adhesion formation [24]. Inflammatory responses stimulate fibrin deposition in the injured area and promote the conversion of mesothelial cells into mesenchymal cells, leading to the formation of dense adhesions. TNF- α , a proinflammatory cytokine, shows a role in adhesion formation [25, 26], and TNF- α antagonists also reduce intra-abdominal adhesions [27]. In the present study, the levels of inflammatory cytokines (TNF- α and IL-1 β) in the control group increased significantly following adhesion induction. Combining Enalapril and meloxicam significantly reduced these inflammatory markers. Bayhan *et al.* reported that *pirfenidone prevents the development of intra-abdominal adhesions by reducing TNF- α and TGFB-1* [28]. In addition, it has been reported that vitamin D exerts anti-inflammatory effects by modulating the NF κ B pathway and decreasing the expression of IL-1 β , IL-6, and TNF- α [29]. Enalapril, an angiotensin-converting enzyme inhibitor, has significant potential to reduce inflammation and decrease scar tissue by blocking the renin-angiotensin system. Enalapril improves tubulointerstitial damage and inhibits interstitial inflammation in nephropathic rats by decreasing NLRP3 inflammasome expression, caspase-1, IL-1 β , and IL-18 [30], and inhibits paraquat-induced pulmonary inflammation and fibrosis [31]. Karimian *et al.* demonstrated that Enalapril reduces fibrosis and lipid peroxidation in rats' liver tissue in a model of bile duct obstruction [32]. Even chronic administration of Enalapril reduces proinflammatory cytokines such as IL-1 β in male and female mice at advanced age [33]. Therefore, the results of the present study are consistent with other research. It has been emphasised that oxidative stress plays an important role in angiogenesis and fibrosis by stimulating fibroblast proliferation in the injured area [34]. Conversely, antioxidant agents such as vitamin E may help prevent peritoneal adhesions after surgery [35]. Accordingly, MDA and some antioxidant

enzymes were measured in the adhesion tissue. The antioxidant effects of captopril and Enalapril on reactive oxygen species-induced endothelial dysfunction in the rabbit abdominal aorta were investigated, and the researchers reported that this protective effect was associated with inhibition of superoxide anions [36]. Lisinopril and Enalapril significantly reduced MDA levels and increased total antioxidant capacity in doxorubicin-induced acute kidney injury in male Wistar rats [37]. In examining the Effect of Enalapril on the growth rate of broiler chickens, significant decreases in MDA levels and increases in antioxidant enzymes, such as SOD and GPx, were observed [38]. These are consistent with the antioxidant and anti-inflammatory effects of other drugs studied in the prevention of intra-abdominal adhesions. Previous studies have suggested that many antioxidants can prevent intra-abdominal adhesions, including lycopene [39], emodin [40], *the hydroalcoholic extract of Dracocephalum kotschy* [41], and galbanic acid [42]. This effect depends on scavenging free radicals. Punica granatum seed oil, an antioxidant, anti-inflammatory, antifibrotic, and antiangiogenic agent, decreases peritoneal adhesion and reduces MDA and TNF- α and IL-1 β gene expression (8). In the present study, although adhesion induction caused a significant increase in MDA, the levels of antioxidant enzymes, such as SOD, GPX, and CAT, were reduced, indicating their involvement in oxidative stress inhibition at the surgical site. The administration of Enalapril and meloxicam not only significantly reduced malondialdehyde (MDA) levels but also markedly increased antioxidant enzyme activity. This is consistent with the results of other studies. The results of the present study also showed that although meloxicam alone reduced inflammation, oxidative stress, and tissue fibrosis, it was not significantly effective in preventing adhesion formation. The administration of two drugs, meloxicam and Enalapril, had a synergistic effect, resulting in better reductions in inflammation, inhibition of oxidative stress, and decreased adhesion formation. These are consistent with other studies.

4. Conclusion

Intra-abdominal adhesion formation is driven by complex processes including inflammation, oxidative

stress, impaired fibrinolysis, and fibroblast proliferation. While the individual administration of Enalapril (an ACE inhibitor) or meloxicam (an NSAID) demonstrated partial efficacy in reducing specific pathological markers like tissue fibrosis, inflammation, bleeding, oxidative stress (MDA), and proinflammatory cytokines (TNF- α , IL-1 β) in this rabbit model, neither drug alone significantly reduced the actual occurrence or severity of postoperative adhesions. Crucially, the coadministration of Enalapril and meloxicam proved significantly more effective, successfully reducing both the incidence and severity of adhesions. This synergistic effect likely stems from their combined potentiation of anti-inflammatory, antioxidant, and antifibrotic actions – specifically, the marked reduction in TNF- α and IL-1 β , decreased MDA levels, enhanced antioxidant enzyme activity (SOD, GPX, CAT), and inhibition of collagen deposition. These findings strongly support the potential of combined ACE inhibitor and NSAID therapy as a promising strategy for preventing postoperative intra-abdominal adhesions.

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Conflict of interest

All authors have declared no conflicts of interest.

Data availability

Data is available upon request from the corresponding author.

Authors Contributions

F.S and E.V. designed the experiments and supervised all steps of the study. E.M and M.A. performed the experiments. F.S and M.N analysed the data and wrote the original manuscript. All authors approved the final submitted version of the manuscript.

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Using artificial intelligence chatbots

There was no use of artificial intelligence in the making of this article.

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