

# Molsidomine (MOL) reduces postoperative pelvic adhesion: A rat uterine horn model

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## Abstract

**Aim:** Postoperative pelvic adhesions (PPAs) are a common complication that leads to many problems. This study aimed to compare the role of Seprafilm (a protective barrier), and molsidomine (MOL), recognized for its antioxidative and antiproliferative effects, in preventing pelvic adhesion.

**Material and Methods:** A total of 30 of female Wistar albino rats were randomly divided into 3 groups. They underwent bilateral uterine horn injury. The rats in the Sham group (n=10) received no special treatment. The rats in the Seprafilm group (n=10) were treated with Seprafilm. The rats in the MOL group (n=10) received 10 mg/kg MOL orally for 14 days. Adhesion scores were evaluated using macroscopic, microscopic, and immunohistochemical grading 14 days postoperatively.

**Results:** The Majuzi adhesion score of the rats in the MOL group [1 (0-4)] was lower than the score of the rats in the sham [4 (2-5)] and Seprafilm [4 (1-5)] (p<0.05). The glutathione peroxidase level in the MOL group [9.34 (5.45 - 19.82)] was higher than that in the sham [7.05 (2.67 - 8.9)] and Seprafilm [5.85 (3.92 - 22.55)] groups (p<0.05).

**Conclusions:** This study showed that MOL reduced the formation of PPAs in a rat uterine horn model. The need for larger studies is an obvious need to elucidate this issue.

**Keywords:** Seprafilm; Hyaluronic Acid; Molsidomine; Pelvic Adhesions.

## INTRODUCTION

About 50%–95% of patients who undergo pelvic surgery develop intra-abdominal adhesion (1). PPAs can lead to many adverse consequences, including intestinal obstruction, infertility, difficulty in a subsequent surgery, and chronic pelvic pain. Repeated surgery can be difficult due to the adhesions and PPAs also results in financial loss. A study from Switzerland estimated the annual cost of PPAs as 13 million USD (2). A 1994 USA study reported a 1.3 billion cost for adhesiolysis surgeries in the study year (3). Various drugs such as antibiotics, fibrinolytic agents (streptokinase and urokinase), nonsteroidal anti-inflammatory drugs, colchicine, vitamins, corticosteroids, and calcium channel blockers and Seprafilm [modified sodium hyaluronate (HA) and carboxymethylcellulose

(CMC)] have been investigated to prevent PPAs in animal models and the clinical trials but only a few of them in use in daily practice (4).

Oxidative stress and the inflammation in the surgical lesions and in the peritoneal cavity have an important role in adhesion formation by slowing down the repair process (5). Normally, reactive oxidative and nitrogen species (ROS/RNS) are removed by antioxidant system in the cells. Excessive ROS/RNS production can exceed the capacity of the endogenous antioxidant system and thereby cause to cell damage (6).

Nitric oxide (NO) is critical for regulating vascular hemodynamics and protecting cells from inflammation, oxidation and procoagulant stimuli. NO and some of its derivatives scavenge ROS/RNS and inhibit expression

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of cellular adhesion molecules, platelet aggregation and leukocyte adhesion which are cytotoxic and vasoconstrictor products, and cause the progression of inflammation (7). Molsidomine (MOL) is transformed into the metabolite 3-morpholinonydnimine (SIN-1) in the liver and widely used as a vasodilating and antianginal agent. In vivo SIN-1 is converted from peroxyntirite donor to a (NO) donor in aerobic solutions (8). NO donor MOL has been shown to exert powerful antioxidant and anti-inflammatory effects (9-11).

Septrafilm adhesion barrier is a mechanical bioresorbable membrane comprising two polysaccharides (HA+CMC). Septrafilm has been approved by the Food and Drug Administration (FDA) since 1996 as an adhesion barrier and is available worldwide. However, covering and fixing them on the tissue with an irregular shape is difficult (12,13).

The Medline, PubMed, and Scopus databases were searched for English-language studies published between January 1990 and March 2018, using combinations of search terms related to PPAs and MOL. No investigation of the role of MOL against PPAs is available in the literature yet. Therefore, this study aimed to explore whether the MOL has an effect on the prevention of pelvic adhesion.

## MATERIAL and METHODS

A total of 30 female Wistar albino rats, aged 10–12 weeks of age and weighing 250–300 g, were used in this study. The rats were housed in Inonu University Animal Experiments Center at 22°C and 60% ± 5% humidity with a 12-h dark and 12-h light cycle (light on from 07 a.m.-19 p.m.). They were randomly divided into 3 groups (n=10). They were provided with food and water ad libitum and fed with standard rat food. All experiments in this study were conducted in accordance with the Directive of the National Institute of Health Animal Research and approved by the Inonu University Animal Research Committee (2014/A-91). The minimum sample size per group was calculated as 10 for the comparison of 3 groups by NCSS PASS 13 program (with an estimated impact width of 0.6236, 95% confidence level, and 80% strength) (14).

### Surgical procedure

All rats were fasted overnight before the surgery. They were anesthetized with an injection of 50 mg/kg ketamine (Ketalar®, Pfizer, Turkey) and 10 mg/kg xylazine HCl (Rompun®, Bayer, Turkey). All surgical procedures were performed under sterile conditions, and antibiotics were not administered to the rats before or after the surgery. Following general anesthesia, the rats were placed in a supine position on the operating table; the abdominal areas of the rats were shaved and disinfected with povidone-iodine solution. A midline incision was made 3 cm in length, and the uterine horns were exposed. Five standard lesions were applied on the antimesenteric surface of each uterine horn using 10-W bipolar cautery. After surgery, the first group received no treatment and was named the sham group (n=10). The second group was named the Septrafilm

group (n=10); in addition to the standard procedure, 2 x 1 cm<sup>2</sup> Septrafilm (Genzyme Biosurgery, Framingham, MA, USA) was placed between the uterus and the abdominal wall of these rats. The third group was named the MOL group (n=10); MOL (Molsicortb® 10 mg, Sandoz, Turkey, 10 mg/kg daily) was given to these rats for 14 days by orogastric gavage. The dose of MOL was adjusted considering the antioxidant activity in previous studies in rats (6,7). All rats were sacrificed after administering a high dose of anesthesia on day 14 after the operation. Laparotomy was performed, and the rats were assessed in terms of initial laparotomy scar, abdominal wall, and uterine horn stickiness. Tissue samples were collected from all of the adhesions and the peritoneal surfaces. An amount of tissue samples were placed in formaldehyde solution for routine histopathologic examination and an amount of tissue samples were stored at 85°C until assayed for biochemical analyses.

### Macroscopic evaluation

Adhesions were graded according to the Mazuji classification system (15) (Figure 1) (Table 1). The macroscopic evaluation was performed by an experienced surgeon with no knowledge about the groups.



**Figure 1.** Formation of adhesion with different grade. a: grade 1 adhesion (extremely small); b: grade 2 adhesion (easily separable); c: grade 4 adhesion (not easily separable)

**Table 1. Majuzi classification system**

Grade	Description of grade
0	No adhesion
1	Extremely small, irregular adhesion
2	Easily separable, medium-intensity adhesion
3	Intense, not easily separable regular adhesion
4	Extremely intense, not easily separable, homogeneous adhesion

### Histopathological evaluation

Tissue specimens collected from between the abdominal wall peritoneum and uterine horns of the three groups of rats were fixed in 10% formaldehyde buffer solution for 24 h. Following routine tissue sampling, the tissue samples were embedded in paraffin blocks. Tissue sections (5-mm-thick) were taken, stained with hematoxylin and eosin, and evaluated using a light microscope at 100x magnification. Histopathological evaluation was performed using a semi-quantitative scoring system (Table 2).

### Biochemical evaluations

Superoxide dismutase (SOD) activity was determined using the nitroblue tetrazolium (NBT) test, which was defined by Sun et al. and modified by Durak et al. (16-

17). The superoxide radicals produced by the xanthine/xanthine oxidase system reduced NBT and formed colored formazans in this method. These colored formazans showed maximum absorbance at 560 nm. The results were evaluated using a spectrophotometer. One SOD unit is the enzyme activity that inhibits NMT reduction by 50%. The results are expressed as U/mg protein.

Grade	Description	Grade	Description
0	Nil	Nil	Nil
1	Grant cells, occasionally scattered lymphocytes, and plasma cells	Minimal, loose	
2	Grant cells with increased numbers of admixed lymphocytes, plasma cells, eosinophils and neutrophils	Moderate	
3	Many admixed inflammatory cells and microabscesses	Florid, dense	

Reduced glutathione (GSH) concentration was measured according to the method developed by Beutler et al. (18). The GSH level measurement was based on the measurement at 412 nm of the yellow color created by the sulfhydryl groups with 5,5'-dithiobis-(2-nitrobenzoic acid) (Ellmann's solution). The GSH level was expressed as  $\mu\text{mol/g}$  protein.

Determination of malondialdehyde (MDA) production method which developed by Esterbauer and Cheeseman was used because it is the most commonly used peroxidation determination method. MDA and other thiobarbituric acid reactive substances that react with thiobarbituric acid in an acidic environment at 90–95<sup>o</sup> formed pink-colored chromogens. The specimens were boiled for 15 min and then rapidly cooled. The absorbance was read using a spectrophotometer at 532 nm. For calculation, the standards prepared at various concentrations from a 20mM/L stock standard solution underwent the same procedures as the samples, and a standard graph was produced with the results. The slope constant from this graph was applied to the specimens, and the MDA amount was calculated as nanomoles per gram of wet tissue.

Glutathione peroxidase (GSH-Px) activity was measured using the method defined by Paglia et al. (19). GSH-Px catalyzed the conversion of GSH in the presence of hydrogen peroxide into oxidized glutathione (GSSG). Further, GSSG produced in a hydrogen peroxide medium by GSH-Px was reduced to GSH with the help of glutathione reductase and nicotinamide adenine dinucleotide phosphate (NADPH). GSH-Px activity was calculated by measuring the decrease in absorbance during the oxidation of NADPH to NADP<sup>+</sup> at 340 nm.

#### Statistical evaluation

The Shapiro–Wilk test was used to determine the conformance of the data with a normal distribution. The data were summarized with medians and minimum and maximum values. The Kruskal–Wallis test was used for comparisons, followed by the Conover pairwise comparison method. The significance level was set at 0.05 for all tests.

## RESULTS

No rat died during or after surgery in this study. Moreover, no postsurgical infection was found on the incision areas. Significant differences in Majuzi adhesion score were found between the MOL, Sham and Seprafilm groups (Table 3). The adhesion score in the MOL group was lower than the score those in the Sham and Seprafilm groups ( $P < 0.05$ ). No difference in adhesion score was observed between the Sham and Seprafilm groups.

No differences in histological scoring according to inflammation, fibroblastic activity, foreign body reaction, vascular proliferation, and collagen formation were found between the groups (Table 3).

**Table 3. Comparison of Majuzi adhesion score, histological features and biochemical differences between groups**

	Group	Median Foreign body (Min.-Max.)	p
<b>Macroscopical Majuzi adhesion score</b>	Sham <sup>†</sup>	4 (2-5)	0.004
	Seprafilm <sup>†</sup>	4 (1-5)	
	Mol <sup>‡</sup>	1 (0-4)	
<b>Histological Fibroblastic activity</b>	Sham	1 (0 - 3)	0.092
	Seprafilm	2.5 (1 - 3)	
	Mol	1.5 (1 - 3)	
<b>Foreign body</b>	Sham	1 (0 - 3)	0.412
	Seprafilm	2 (0 - 3)	
	Mol	1.5 (0 - 3)	
<b>Vascular proliferation</b>	Sham	1.5 (0 - 3)	0.096
	Seprafilm	2 (1 - 2)	
	Mol	1 (0 - 3)	
<b>Collagen formation</b>	Sham	1 (0 - 2)	0.324
	Seprafilm	1 (0 - 2)	
	Mol	0.5 (0 - 2)	
<b>Inflammation</b>	Sham	1.5 (0 - 3)	0.240
	Seprafilm	2 (1 - 3)	
	Mol	1 (0 - 2)	
<b>Biochemical SOD (U/mg protein)</b>	Sham	0.11 (0.1 - 0.14)	0.052
	Seprafilm	0.08 (0.04 - 0.38)	
	Mol	0.09 (0.06 - 0.16)	
<b>GSH (nmol/g wet tissue)</b>	Sham	207.4 (142.3 - 306.3)	0.095
	Seprafilm	300 (135 - 397.14)	
	Mol	268.3 (188 - 696.2)	
<b>GSH-Px (U/g protein)</b>	Sham <sup>†</sup>	7.05 (2.67 - 8.9)	0.033
	Seprafilm <sup>†</sup>	5.85 (3.92 - 22.55)	
	Mol <sup>‡</sup>	9.34 (5.45 - 19.82)	
<b>MDA (nmol/g protein)</b>	Sham	9 (3.6 - 20.9)	0.133
	Seprafilm	10.4 (4.0 - 27.7)	
	Mol	5.9 (2.4 - 24.5)	

Min: minimum. Max: maximum. <sup>†‡</sup>: Medians that do not share a symbol are significantly different

In biochemical results, GSH-Px level in the MOL group was higher than those in the Sham and Seprafilm groups ( $P=0.027$ ). No differences in GSH and MDA levels were observed between the MOL, Sham, and Seprafilm groups (Table 3).

## DISCUSSION

In our study, we showed that only GSH-Px level is higher in the MOL group than the others and Majuzi adhesion score was lower in the MOL group compared with the Seprafilm and Sham groups ( $P=0.004$ ). The low Majuzi adhesion score in the MOL group might be the result of the antioxidant levels that increased with MOL and the resulting anti-inflammatory and anti-adhesion effects. Many studies have shown that MOL is a strong antioxidant, antiapoptotic and has anti-inflammatory effects (20-22). NO and its derivatives remove ROS/RNS from the media and inhibit platelet aggregation, leukocyte adhesion, and expression of cellular adhesion molecules (23).

The pathophysiology of PPAs includes inflammation of the peritoneal surfaces, which develops due to a traumatic insult such as surgery, infection, or radiation. A large number of fibroblasts migrate to the wound region during the inflammation and start the proliferation phase characterized by collagen production and storage together with angiogenesis. They secrete collagen and fibronectin to create an extracellular matrix, leading to the development of fibrous bands between the tissues. This extracellular matrix is degraded by matrix metalloproteinase (MMP). If MMP is inhibited, the extracellular matrix cannot be degraded and adhesions bands develop between the tissues. The synthesized ROS/RNS play an important role in this process, but they also increase inflammation due to the damage they cause in the surrounding tissues and contribute to adhesion development (4,23). Molecules such as GSH, GSH-Px, SOD, and catalase have antioxidant properties and they are produced by the cell. Antioxidants keep ROS in low levels. In the inflammation process, NO reacts with ROS and RNS occur. ROS induces expression of genes in cells that produce antioxidants (20). Both GSH-Px and SOD decrease the lipid peroxidation of biological membranes. GSH-Px is responsible from detoxification of hydrogen peroxide. SOD catalyzes the dismutation of superoxide anion to hydrogen peroxide and molecular oxygen and superoxide anion becomes less hazardous (23).

It is well known that in the liver, MOL decarboxylases enzymatically to SIN-1, which spontaneously releases NO (24,25). NO is crucial in inflammation, cell defense, and tissue injury (9). NO increases the levels of cyclic guanosine monophosphate, decreases the levels of intracellular calcium ions, leads to the relaxation of smooth muscle vasculature, inhibits platelet aggregation, and has an indirect antiproliferative effect on smooth muscle cells. MOL belongs to the drug class of sydnonones. The indications for MOL are as follows; chronic heart failure, ischemic heart disease, and pulmonary hypertension (26). No effect of tolerance to the drug observed in

observational clinical studies (27). Also, MOL has been shown to reduce neutrophil involvement in the peritoneum and lungs during peritonitis (23). Given the protective and therapeutic effects of MOL on bleomycin-induced pulmonary fibrosis, MOL application (before and after bleomycin administration) has been reported to increase total antioxidant levels reduced by bleomycin (25). In a previous study, biochemical and histopathological evaluations of kidneys showed that MOL inhibited the toxic effects of cisplatin by acting as a potent anti-inflammatory and antiapoptotic agent that removed free radicals from the environment (28). But the limitation of this study is we could not evaluate any anti-inflammatory effect of MOL by histologically via specific kits. Fibroblastic activity score, foreign body reaction score, vascular proliferation score, and collagen formation score were not found as different among the groups.

The method to prevent PPAs should be easy to apply and associated with little or no side effects and low cost for widespread acceptance. Oral MOL may, therefore, find wide usage for PPAs prevention because it does not require special storage conditions and is less expensive. In 1996, Seprafilm Adhesion Barrier received the approval of the FDA and was suitable for the use by patients undergoing abdominal or pelvic laparotomy. To date, Seprafilm has been used for more than two million patients to reduce the incidence, prevalence, and severity of postoperative adhesions between organs such as the omentum, small intestine, bladder, and stomach, between the abdominal wall and the abdominal cavity, and between the uterus and tubes and the surrounding structures such as the ovary, large intestine, and bladder (29). Zeng et al. mentioned the reliability and effectiveness of Seprafilm in a systematic review and meta-analysis. Analyses have shown that HA/CMC (Seprafilm) can reduce abdominal adhesions after abdominal surgery (30). Seprafilm is perhaps the most studied material to prevent intra-abdominal adhesions. Numerous animal studies have been conducted to investigate the efficacy and safety of Seprafilm in preventing postoperative abdominal adhesions (30-32). A prospective, randomized controlled study contradicted the findings of other studies (33). They reported that intraoperative adhesion scores were not different between the groups. The morphological, histological, and biochemical results of this study indicated that the PPAs-protective effect of Seprafilm was not observed.

## CONCLUSION

Another important finding of the present study is that no toxic or lethal effects of MOL are found in this study. The second limitation of the study was that the protective effect of MOL was not compared using different doses. Therefore, a possible dose-dependent relationship between the anti-adhesive effect and any toxic complications of MOL could not be assessed.

The present study demonstrated a protective effect of MOL on PPAs in a uterine horn rat model by macroscopically and biochemically. However, we could not demonstrate the

anti-adhesive effect of MOL by histologically. Additional clinical and experimental studies are required to confirm the findings before initiating the clinical use of MOL for preventing PPAs.

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## REFERENCES

- Drollette CM, Badawy SZ. Pathophysiology of pelvic adhesions. modern trends in preventing infertility. J Reprod Med 1992;37:107-21.
- Ivarsson ML, Holmdahl L, Franzén G, et al. Cost of bowel obstruction resulting from adhesions. Eur J Surg 1997;163:679-84.
- Ray NF, Denton WG, Thamer M, et al. Abdominal Adhesiolysis: Inpatient Care and Expenditures in the United States in 1994. J Am Coll Surg 1998;186:1-9.
- Arung W, Meurisse M, Detry O. Pathophysiology and prevention of postoperative peritoneal adhesions. World J Gastroenterol 2011;17:4545.
- Koninckx PR, Gomel V. Introduction. quality of pelvic surgery and postoperative adhesions fertilsteril 2016;106:991-3.
- Polat N, Ozer MA, Parlakpınar H, et al. Effects of molsidomine on retinal ischemia/reperfusion injury in rabbits. Biotech Histochem 2018;93:188-97.
- Durak MA, Parlakpınar H, Polat A, et al. Protective and therapeutic effects of molsidomine on radiation induced neural injury in rats Biotech Histochem 2017;92:68-77.
- Singh RJ, Hogg N, Joseph J, et al. The peroxynitrite generator, sin-1, becomes a nitric oxide donor in the presence of electron acceptors. arch biochembiophys 1999;361:331-9.
- Gupta A, Sharma S, Chopra K. Reversal of iron-induced nephrotoxicity in rats by molsidomine, a nitric oxide donor. Food Chem Toxicol 2008;46:537-43.
- Walder CE, Thiemermann C, Vane JR. The involvement of endothelium-derived relaxing factor in the regulation of renal cortical blood flow in the rat. Br J Pharmacol 1991;102:967-73.
- Kalouda T, Pitsikas N. The nitric oxide donor molsidomine induces anxiolytic-like behaviour in two different rat models of anxiety. Pharmacol Biochem Behav 2015;138:111-6.
- Lee JH, Go AK, Oh SH, et al. Tissue anti-adhesion potential of ibuprofen-loaded PLLA-PEG diblock copolymer films. Biomaterials 2005;26:671-8.
- Shahram E, Sadraie SH, Kaka G, et al. Evaluation of chitosan-gelatin films for use as postoperative adhesion barrier in rat cecum model. Int J Surg 2013;11:1097-102.
- Karatas A, Ozlu T, Ozyalvacli G, et al. Intraperitoneal nigella sativa for prevention of postoperative intra-abdominal adhesions in rats. J Invest Surg 2014;27:319-26.
- Mazuji Mk, Kalambaheti K, Pawar B. Prevention of Adhesions With Polyvinylpyrrolidone. Arch Surg 1964;89:1011-5.
- Sun Y, Oberley LW, Li Y. A simple method for clinical assay of superoxide dismutase. Clin Chem 1988;34:497-500.
- Durak I, Akyol O, Es MU, et al. Element structure in stenotic mitral valves. Am J Cardiol 1993;71:355.
- Beutler E, Duron O, Kelly Bm. Improved method for the determination of blood glutathione. J Lab Clin Med 1963;61:882-8.
- Esterbauer H, Cheeseman KH. Determination of aldehydic lipid peroxidation products: malonaldehyde and 4-hydroxynonenal. Methods Enzymol 1990;186:407-21.
- Soneja A, Drews M, Malinski T. Role of nitric oxide, nitroxidative and oxidative stress in wound healing. Pharmacol Rep 2005;57:10-9.
- Kukovetz WR, Holzmann S. Cyclic GMP as the mediator of molsidomine-induced vasodilatation. Eur J Pharmacol 1986;122:103-9.
- Chander V, Chopra K. Renal Protective Effect of Molsidomine and L-Arginine in Ischemia-Reperfusion Induced Injury in Rats. J Surg Res 2005;128:132-9.
- Fukatsu K, Saito H, Han I, et al. Nitric oxide donor decreases neutrophil adhesion in both lung and peritoneum during peritonitis. J Surg Res 1998;74:119-24.
- Disli OM, Sarihan E, Colak MC, et al. Effects of molsidomine against doxorubicin-induced cardiotoxicity in rats. Eur Surg Res 2013;51:79-90.
- Kilic T, Parlakpınar H, Polat A, et al. Protective and therapeutic effect of molsidomine on bleomycin-induced lung fibrosis in rats. Inflammation. 2014;37:1167-78.
- Kmieć M, Ochmański W. Molsidomine: importance in treatment of circulation disorders. Przegl Lek 1998;55:532-6.
- Messin R, Karpov Y, Baikova N, et al. Short- and long-term effects of molsidomine retard and molsidomine nonretard on exercise capacity and clinical status in patients with stable angina: a multicenter randomized double-blind crossover placebo-controlled trial. J Cardiovasc Pharmacol 1998;31:271-6.
- Karakoc HT, Altintas R, Parlakpınar H, et al. Protective effects of molsidomine against cisplatin-induced nephrotoxicity. Adv Clin Exp Med 2015;24:585-93.
- Diamond MP, Burns EL, Accomando B, et al. Sefrafilm® adhesion barrier: (1) a review of preclinical, animal, and human investigational studies. Gynecol Surg 2012;9:237-45.
- Zeng Q, Yu Z, You J, et al. Efficacy and safety of seprafilm for preventing postoperative abdominal adhesion: systematic review and meta-analysis. World J Surg 2007;31:2125-31.
- Eroglu A, Demirci S, Kurtman C, et al. Prevention of intra-abdominal adhesions by using seprafilm in rats undergoing bowel resection and radiation therapy. Color Dis 2001;3:33-7.
- Oncel M, Remzi FH, Senagore AJ, et al. Application of Adcon-P or Sefrafilm in consecutive laparotomies using a murine model. Am J Surg 2004;187:304-8.
- Stawicki SP, Green JM, Martin ND, et al. Results of a prospective, randomized, controlled study of the use of carboxymethylcellulose sodium hyaluronate adhesion barrier in trauma open abdomens. Surg 2014;156:419-30.