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Research Article

The Effect of Hypochlorous Acid on Preventing Postoperative Peritoneal Adhesions: An Experimental Study

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Abstract

Objectives: Postoperative peritoneal adhesion is a devastating complication without an ideal preventive and therapeutic modality. There is controversy about the effect of hypochlorous acid solutions and whether they contribute to the development or prevention of experimental peritoneal adhesions, given their anti-inflammatory and microbicidal properties. Therefore, the objective of this study is to evaluate the effect of the intraperitoneal hypochlorous acid application on the extension and severity of peritoneal adhesions in an experimental model.

Methods: A total of 24 Wistar-albino rats were divided into three groups: Group 1 (Sham surgery), Group 2 (peritoneal adhesion using cecal serosal abrasion with parietal peritoneal excision and intraperitoneal saline), and Group 3 (peritoneal adhesion using cecal serosal abrasion with parietal peritoneal excision and intraperitoneal hypochlorous acid). On the postoperative 14th day, abdominal cavities were explored. Linsky's and Knightly's macroscopic adhesion classifications reflected the extent and intensity of adhesions. Zühlke's classification was used to grade the adhesions microscopically.

Results: Animals in all groups developed cecal and peritoneal adhesions to variable extents and at various severity levels, except for two (28.6%) animals in Group 3. Nevertheless, there was no significant difference between the groups in scores obtained from the Linsky's peritoneal adhesion extent classification, the Knightly's peritoneal adhesion severity classification, and the Zuhlke's microscopic adhesion classification systems ($p>0.05$ for all).

Conclusion: Intraperitoneal hypochlorous acid application did not lead to any significant improvement in the macroscopic and microscopic peritoneal adhesion scores.

Keywords: Surgical adhesions, intraperitoneal injections, hypochlorous acid, experimental model

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Postoperative peritoneal adhesions are critical clinical situations that develop following most abdominal surgeries.[1] Inadequate healing of the peritoneum leads to fibrous scar tissue, which causes adhesion formation after abdominal surgical procedures.[2] Due to the adhesions 'localization and severity, chronic abdominopelvic pain and intestinal obstruction may be experienced during the postoperative period.[1-3] Given the difficulty in treating the sequelae and high recurrence rates of peritoneal adhesions, prophylactic approaches that aim to prevent adhesions are considered more effective than the therapeutic approaches that aim to treat the adhesions.[1]

An ideal prophylactic modality that aims to prevent peritoneal adhesions should reduce or eliminate adhesions, not disrupt the wound healing process, and exert its effects lo-

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cally without giving rise to any side effects. In this context, various biomaterials and physical formulations were investigated in several clinical and experimental studies.[1] In addition, several drugs or substances that act on coagulation, inflammation, and fibrinolysis have been employed to produce an anti-adhesion effect. However, there is still no established definitive and effective modality for preventing and treating adhesions. Thus, there is a need for a novel method that reduces or prevents peritoneal adhesion.[4,5]

Hypochlorous acid (HClO) solutions have been used in hospitals, animal facilities, and food-packaging plants due to their disinfectant feature.[6] Hypochlorous acid is a weak acid formed via electrolysis of sodium hypochlorite and hydrochloric acid in tap water.[7] Previous studies reported the efficiency of HClO against several microorganisms and clinical conditions caused by these microorganisms.[6,8] Experimental studies demonstrated a reduction in activity with oral or intraluminal use of hypochlorous acid, allowing its direct contact with the organic material within the stomach and intestine.[6] The production of reactive oxygen species and hypochlorite is related to the native immune response of the organisms during the inflammation process of the peritoneal injury.[1]

Intraperitoneal application of sodium hypochlorite (NaOCl) leads to sterile peritonitis secondary to sterile transient chemical injury.[9] Depending on the dosage of sodium hypochlorite, pronounced fibrosis and thickening of parietal peritoneum or visceral organs reportedly developed following intraperitoneal application in pigs.[10] Fibroplasia develops on peritoneal surfaces, and the inflammatory injury increases the lymphatic absorption from the peritoneal surfaces. Levine et al. carried out an experimental model using sodium hypochlorite to determine the additive and adaptive responses to repeated peritoneal injury.[9] Although single and diluted intraperitoneal injection caused no change in the peritoneal morphological characteristics, they showed a dose-dependent effect of sodium hypochlorite on the development of peritoneal fibrosis. All in all, the preventive or causative effect of HClO remains controversial. Therefore, the objective of this study is to evaluate the effect of HClO in preventing postoperative peritoneal adhesions in an experimental model.

Methods

Research Design

This experimental study was designed to evaluate the anti-adhesive effect of HClO in a peritoneal adhesion model using cecal serosal abrasion with parietal peritoneal excision. Aydın Adnan Menderes University Experimental Animal Studies Local Ethical committee approved the study protocol (June 29th, 2018, 2018/077). All animals were supplied from Aydın Adnan Menderes University, Faculty of Veterinary Medicine, Laboratory of Experimental Animals. The researchers agreed to apply the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (ETS123).

Twenty-four young, Wistar-albino rats weighing 300-400 grams were used in the experiment. All animals were housed under standard conditions, fed with a standard diet, and allowed ad libitum access to food and water.

Surgical Procedures

All animals were fasted for 12 hours and operated on under sterile conditions by the same research team. Ketamine (Ketalar®, intramuscular, 50 mg/kg, Pfizer, U.S.) and xylazine (Rompun®, intramuscular, 10 mg/kg, Bayer, Istanbul, Turkey) were used to induce general anesthesia and analgesia. The animals were placed in the supine position during the surgical procedures. The abdominal wall of each rat was shaved and cleaned using a 10% povidone-iodine solution. A 3 cm-long midline incision was made, and cecal and peritoneal adhesion models were applied to each animal. The cecal abrasion was made using a sterile brush over the anterior cecal serosal tissues, causing subserosal petechial bleedings.[11] In addition, 1 cm2 of parietal peritoneum was excised at the right lower quadrant for the peritoneal adhesion model.[12]

The animals were randomized into three groups after the formation of the experimental adhesion model:

Group 1 (n=8): Sham group rats underwent standard adhesion modeling and received no medical therapy.

Group 2 (n=8): Abdominal washing was applied via intraperitoneal 100 ml/kg standard saline solution followed by aspiration after 5 minutes.

Group 3 (n=8): Abdominal washing was applied via intraperitoneal 100 ml/kg of commercially available stabilized HClO solution, which was generated from the reverse reaction of NaOCl and hydrogen peroxide, followed by aspiration after 5 minutes. The chemical properties of the HClO solution were as follows: Concentration: 218 ppm, pH: 7.1, ORP (oxidation-reduction potential): 871 mV, shelf-life: 24 months (NPS Biocidal, Istanbul, Turkey).[13,14]

Following the surgical procedures, the abdominal layers were closed via continuous suturing using 3/0 absorbable vicryl sutures. Non-absorbable 4/0 polypropylene sutures were used to close the skin. The animals were continuously monitored until they were fully awakened. Subsequently, they were transferred to the cages in which they were fed with full feed. The animals were monitored in the laboratory for 14 days.[15] On the postoperative 12th day, one animal from Group 3 died. The remaining 23 animals were included in the study.

After 14 days, a 3 cm-long new left paramedian incision was made lateral to the previous incision under Ketamine [Ketalar®, intramuscular, 50 mg/kg, Pfizer, Istanbul, Turkey) and xylazine (Rompun®, intramuscular, 10 mg/kg, Bayer, Istanbul, Turkey) anesthesia. 2-cm long transverse incisions were made at the lower and upper borders of the paramedian incision. After lifting the abdominal wall starting from lateral to the midline, the peritoneal fluid samples were obtained in a sterile culture vial for microbiological analysis. The peritoneal fluid samples were diluted via serial dilution using standard saline solution, then inoculated in the blood agar and incubated at 37 °C for 18 hours. The microorganisms were identified by gram staining.

Macroscopic Adhesion Assessment

The abdominal cavities were examined by a single researcher who was blind to the groupings. The extent and intensity of the adhesions were graded according to Linsky's and Knightly's macroscopic adhesion classification systems.[2,5,16,17] (Table 1)

Histology

1 cm full-thickness excisions of the cecum, including the previous serosal abrasion area and the parietal peritoneum as well as the previously excised area, were performed for histopathological analysis. The tissue samples were stored in 10%formalin solutions and analyzed at the University of Health Sciences, Children Health and Surgery Research Center, Pathology Laboratory. The samples were embedded in the paraffin blocks following the tissue processes. 5μm-thick sections of the paraffin blocks were stained using hematoxylin-eosin and Mason's Trichrome. An experienced pathologist who was blind to the groupings examined and scored all samples according to the Zühlke's microscopic adhesion classification.[18,19]

All animals were sacrificed by cervical dislocation while under ketamine and xylazine anesthesia.

Statistical Analysis

GraphPad Prism 6 (GraphPad Prism version 6for Windows, GraphPad Software, La Jolla California U.S., www.graphpad.com) software package was used for statistical analysis. Descriptive data were expressed as mean±standard deviation values in the case of continuous variables with normal distribution and as median with minimum-maximum values in the case of continuous variables without normal distribution. Categorical data were expressed using numbers and percentages. The Shapiro-Wilk, Kolmogorov-Smirnov, and Anderson-Darling tests were used to analyze the normal distribution characteristics of the numerical variables.

The One-Way Analysis of Variance (ANOVA) test was used to compare more than two independent groups where numerical variables were determined to conform to the normal distribution, and the Kruskal Wallis test was used to compare more than two independent groups where numerical variables were determined not to conform to the normal distribution. Additionally, the Tukey test was used to evaluate the differences between the groups in analyses involving non-parametric tests of data that are homogeneous based on their distribution. Probability (p) values of ≤ 0.05 were deemed to indicate statistical significance.

Results

The macroscopic and microscopic assessments of adhesions on the cecum and peritoneum are given in Table 2. In Group 3, two (28.6%) animals without cecal and peritoneal adhesions were assigned zero points based on the Linsky's peritoneal adhesion extent and the Knightly's peritoneal adhesion severity classifications. All other animals developed cecal adhesions to variable extents and

Table 1. The Linsky, Knightly, and Zuhlke adhesion scoring systems

Grade	Linsky extent of peritoneal adhesion scoring	Knightly peritoneal adhesion severity scoring	Zuhlke microscopic adhesion grading
0	No adhesion	Complete absence of adhesions	--
1	Adhesions covering less than 25% of the traumatised area	Single thin, easily separated adhesion	Loose connective tissue, cell-rich, old and new fibrin, fine reticulin fibers
2	Adhesions covering 26-50% of the traumatised area	Less extensive, but weak adhesions, which poorly withstood traction	Connective tissue with cells and capillaries, few collagen fibers
3	Adhesions covering 51-75% of the traumatised area	Numerous, extensive visceral adhesions, without visceroparietal extension	Connective tissue more firm, fewer cells, more vessels, few elastic and smooth muscle fibers
4	Adhesions covering 76-100% of the traumatised area	Extensive, dense adhesions that involved the adjacent mesentery, intestines, and omentum and extended to the abdominal wall	Old firm granulation tissue, cell-poor serosal layers hardly distinguishable

at various severity levels. The most commonly assigned Linsky's peritoneal adhesion extent score for the cecum was four in all groups. However, none of the peritonea in Group 3 was assigned four in Group 3, contrary to the other groups.

There were no significant differences between the groups in terms of Linsky's peritoneal adhesion extent, Knightly's peritoneal adhesion severity, and Zuhlke's microscopic adhesion classification systems(p>0.05) (Table 2) (Fig. 1).

Discussion

The findings of this study did not indicate any macroscopic and microscopic improvement in the peritoneal adhesion scores with the use of intraperitoneal HClO application. The extent and severity of the adhesions on the cecum and peritoneum in the HClO group were less prominent than in the other groups, albeit not statistically significant. The dosage of HClO or the effect of the cecal serosal abrasion with parietal peritoneal excision for peritoneal adhesion

Table 2. Macroscopic and microscopic evaluations of adhesions on the cecum and peritoneum.

Scoring system	Grade	Groups			p
		Group 1 (n=8)	Group 2 (n=8)	Group 3 (n=7)	
Linsky extent of peritoneal adhesion scoring-cecum †					
	0	0 (0.0)	0 (0.0)	2 (28.6)	0.723
	1	1 (12.5)	1 (12.5)	0 (0.0)	
	2	2 (25.0)	2 (25.0)	1 (14.3)	
	3	1 (12.5)	0 (0.0)	0 (0.0)	
	4	4 (50.0)	5 (62.5)	4 (57.1)	
Linsky extent of peritoneal adhesion scoring-peritoneum †					
	0	0 (0.0)	1 (12.5)	1 (14.3)	0.187
	1	2 (25.0)	1 (12.5)	2 (28.6)	
	2	1 (12.5)	0 (0.0)	3 (42.9)	
	3	2 (25.0)	1 (12.5)	1 (14.3)	
	4	3 (37.5)	5 (62.5)	0 (0.0)	
Knightly peritoneal adhesion severity scoring-cecum †					
	0	0 (0.0)	0 (0.0)	2 (28.6)	0.079
	1	0 (0.0)	1 (12.5)	0 (0.0)	
	2	0 (0.0)	4 (50.0)	2 (28.6)	
	3	5 (62.5)	1 (12.5)	2 (28.6)	
	4	3 (37.5)	2 (25.0)	1 (14.3)	
Knightly peritoneal adhesion severity scoring-peritoneum †					
	0	0 (0.0)	1 (12.5)	1 (14.3)	0.162
	1	2 (25.0)	0 (0.0)	0 (0.0)	
	2	1 (12.5)	2 (25.0)	5 (71.4)	
	3	2 (25.0)	3 (37.5)	1 (14.3)	
	4	3 (37.5)	2 (25.0)	0 (0.0)	
Zühlke microscopic adhesion grading-cecum †					
	1	2 (25.0)	6 (75.0)	6 (85.7)	0.210
	2	4 (50.0)	2 (25.0)	1 (14.3)	
	3	2 (25.0)	0 (0.0)	0 (0.0)	
	4	0 (0.0)	0 (0.0)	0 (0.0)	
Zühlke microscopic adhesion grading-peritoneum †					
	1	0 (0.0)	1 (12.5)	0 (0.0)	0.667
	2	0 (0.0)	1 (12.5)	1 (14.3)	
	3	8 (100.0)	4 (50.0)	6 (85.7)	
	4	0 (0.0)	2 (25.0)	0 (0.0)	

†: n (%); Group 1: Sham standard adhesion model without abdominal washing; Group 2: Adhesion modeling followed by abdominal washing via intraperitoneal normal saline; Group 3: Adhesion modeling followed by abdominal washing via intraperitoneal hypochlorous acid.

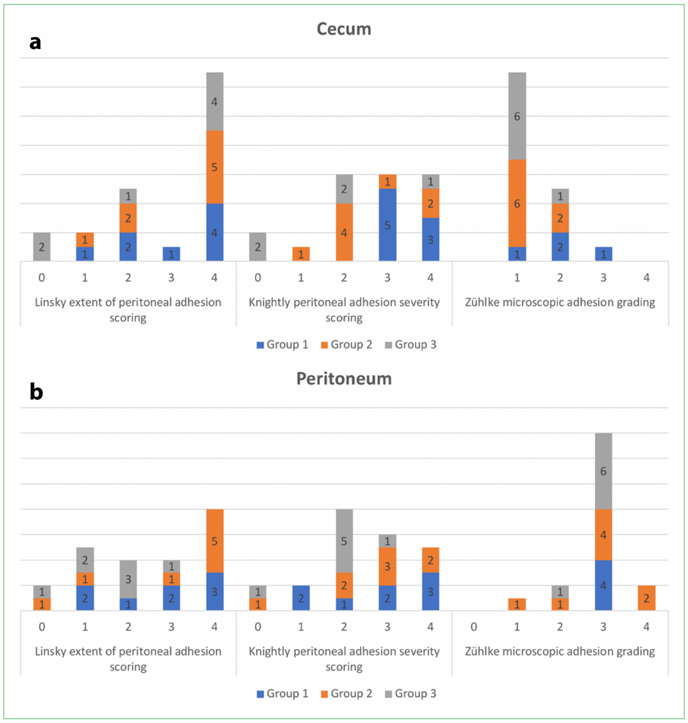

Figure 1. Scores were assigned to **(a)** the cecum and **(b)** the peritoneum based on the Linsky's peritoneal adhesion extent, the Knightly's peritoneal adhesion severity, and the Zühlke's microscopic adhesion scoring systems.

might be the reason for insignificant results.

Peritoneal adhesions occur because of abnormal repair following peritoneal injury.[1] The peritoneum typically has unique defense mechanisms to overcome the noxious pathophysiological events. However, in certain circumstances, the repair mechanisms, including coagulation, inflammation, and fibrinolysis, may not work properly, leading to peritoneal adhesions.[1] Peritoneal adhesions were prevented or eliminated using different molecules with anti-adhesive properties in previous studies.

There were different animal models of peritoneal adhesion available in the literature. The two most frequently studied models to establish severe peritoneal adhesions are the cecum and uterine horn injuries combined with a parietal peritoneum injury.[1] Similarly, the combined injury to the cecum (the cecum-sidewall model) and parietal peritoneum was chosen as the model to be investigated in this study.[18,20] However, there has been some controversy about the efficiency of this model in producing adhesion on the cecum and peritoneum.[2,20] Accordingly, it was speculated that the cecal abrasion might be less consistent in developing adhesions on the cecum than on the peritoneal excision. In contrast, there were no significant differences in the scores assigned to the cecum and peritoneal adhesions between the groups examined within the scope of this study. Therefore, it was concluded that the said model is an effective experimental peritoneal adhesion model.

The selection of laboratory animal strains is another essential factor for the success of the peritoneal adhesion models. Rats are the most widely investigated animal model on this subject, even though they have a higher healing capacity than humans.[1] Therefore, rats are used in this study, given their feasibility and easy accessibility for peritoneal adhesion models.

Visual macroscopic observation is commonly used to evaluate the extent and severity of adhesions; however, the assessment metrics for peritoneal adhesions have been questioned in several studies.[1,18] In this study, Linsky's and Knightly's adhesion classifications, which are among the macroscopic assessment systems, were used.[2,3,5] There are several scoring systems that evaluate adhesions via histopathological examinations, including the Nair's, Swolin's, Zühlke's, and Wlaho's systems.[1,3,18] Each system has its advantages and disadvantages. Therefore, it is important to choose the system that best fits the animal model being used for the experimental study.

The findings of this study did not indicate any improvement in the macroscopic and microscopic peritoneal adhesion scores of the cecum and peritoneum with the use of intraperitoneal HClO. This is the first study to date that investigated the possible anti-adhesive effect of HClO on the peritoneal adhesions. The lack of significant differences might be related to the dosage and frequency of HClO applications. Further studies are needed to demonstrate the possible benefit of HClO in eliminating the peritoneal adhesions.

It was speculated that the reactive oxygen species and hypochlorite might have reciprocal relationships with wound healing.[1] During inflammation, an exaggerated inflammatory response causes the production of metabolites of free oxygen radicals, including hypochlorite, and the resultant increased vascular permeability may trigger the formation of exudates and fibrosis.[1] The resulting peritoneal fibrosis has been demonstrated in the previous experimental studies in which intraperitoneal NaClO has been used.[9,10,21] Nevertheless, further studies are needed to clarify the possible cause-and-effect relationships between reactive oxygen species and the repair process.

The use of solutions containing HClO has been previously investigated in several experimental studies.[8-10] In one of these studies, Hsu et al. demonstrated dose- and time-dependent peritoneal fibrosis following the intraperitoneal application of 15-30mM NaClO in pigs.[10] Intraperitoneal injection of solutions with different concentrations of NaClO resulted in severe fibrosis in tested animals, including adult mice and rats.[9,21] The severity of fibrosis may vary depending on the concentration of hypochlorite and the type of the animal being tested. The differences between the immunological responses of different species to the external stimuli have been blamed for such discrepancies in the literature.[10] It was reported in several studies that repeated stimuli for relatively more extended periods are needed to develop peritoneal fibrosis.[9,22] However, it was also reported that a single administration of NaClO produced severe fibrosis within a week.[9] Therefore, more comprehensive studies are needed to elucidate the causative and reductive action of HClO on peritoneal adhesions.

Based on the bactericidal action mechanisms of HClO, Fernandez et al. applied abdominal washout with HClO in three patients with abdominal sepsis.[7] They concluded that injecting HOCl through the tubing set decreased the need for more frequent abdominal lavage procedures. Previous studies documented the bactericidal activity of HClO against prokaryotic organisms.[7,8,23,24] Kubota et al. showed the effect of peritoneal lavage with electrolyzed strong acid water in achieving further decontamination in an experimental perforated peritonitis model and patients with perforated appendicitis.[14,25] Singal et al. demonstrated the efficacy of peritoneal lavage applied using the super oxidized solution in patients with peritonitis.[26] HClO has been reportedly used in chronic wounds.[6,13,27] The relationship between reactive oxygen species and abdominal cancer cell lines has been another matter of controversy.[28] Among several molecules, it has been shown that HClO has the most potent effects on tumor cells exerted through the promotion of antitumor immunity. In addition, it was demonstrated that HClO had excellent activity against a slimlike biofilm layer produced by prokaryotes for adherence to any surface.[7,8,13,18] The anti-film and anti-cancer effects of HOCl might be beneficial for the prevention of intraperitoneal adhesions.

In this experimental study, HClO was applied intraperitoneally only at a dose of 100 ml/kg. This may be considered a limitation of the study, given that the use of different doses of HClO would have allowed further comparative analyses.

In conclusion, intraperitoneal HClO application did not lead to any significant macroscopic and microscopic improvement in the peritoneal adhesion scores in an experimental model with cecal serosal abrasion with parietal peritoneal excision.

Disclosures

Ethics Committee Approval: Aydın Adnan Menderes University Experimental Animal Studies Local Ethical committee approved the study protocol (June 29th, 2018, 2018/077).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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