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The effect of curcumin on lung injuries in a rat model induced by aspirating gastrointestinal decontamination agents

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Abstract

Background: Aspiration is one of the most feared complications of gastrointestinal decontamination procedures with nonabsorbed polyethylene glycol (PEG) solution and activated charcoal (AC). We aimed to investigate the protective effects of curcumin (CUR) on lung injury in rats induced by aspiration of these agents.

Methods: Experimental rats were divided randomly into 6 groups (n = 7): a saline-aspirated control (group I), sterile saline aspirated with CUR treatment (group II), PEG aspirated (group III), PEG aspirated with CUR treatment (group IV), AC aspirated (group V), and AC aspirated with CUR treatment (group VI). After aspiration, treatment groups II, IV, and VI were given 150 mg/kg CUR intraperitoneally once a day for 7 days. After 7 days, the rats were humanely killed, and both the lungs and serum specimens from all groups were evaluated histopathologically, immunohistochemically, and biochemically.

Results: Aspiration of gastrointestinal decontamination agents produced histopathologic changes, elevated levels of malondialdehyde and surfactant protein D, reduced levels of antioxidant enzymes, and increased expression of inflammatory cytokines interleukin-1β and tumor necrosis factor α. Curcumin treatments effectively attenuated the rats' pulmonary inflammation responses (as shown by reduced alveolar damage), decreased serum malondialdehyde and surfactant protein D levels, and inhibited the expressions of tumor necrosis factor α and interleukin-1β.

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Conclusions: Because of its anti-inflammatory effects, CUR treatment may have preventive effects on lung injuries induced by aspirating gastrointestinal decontamination agents.
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Gastrointestinal decontamination with nonabsorbed polyethylene glycol (PEG) solution and activated charcoal (AC) are modalities used widely by emergency departments in treating patients who ingested toxic agents [1]. These gastrointestinal decontamination agents attempt to interrupt the enterohepatic and enteroenteric circulation of potentially toxic ingestions of sustained-release or enteric-coated drugs [1,2]. Whole bowel irrigation with a PEG solution arguably is the only option for gastrointestinal decontamination in patients presenting more than 2 hours after poisoning, when the amount of poison adsorbed by AC is insignificant [2]. Although PEG and AC are known to be safe and reliable, some complications may occur during or after the use of these agents. One of the most serious complications is aspiration of PEG or AC [3,4]. Therefore, administration of these agents is contraindicated in patients whose airway reflexes are already impaired because of aspiration, or if cerebrovascular accidents, head trauma, seizure, and ingestions are likely to produce central nervous system depression [2].

The pathogenesis and molecular basis of lung injury induced by aspiration have been investigated extensively in recent experimental studies [5,6]. Numerous inflammatory mediators have been reported in lung injury induced by aspirating contents from the gastrointestinal tract. Among these mediators are ICAM-1 (Intercellular Adhesion Molecule-1)/lymphocyte function–associated antigen-1, neutrophil adhesion receptor CD18, interleukins (IL-1β, IL-6, IL-8, and IL-10), macrophage inflammatory proteins-2 and keratinocyte-derived cytokine, monocyte chemoattractant protein-1, tumor necrosis factor (TNF) α, and cytokine-induced neutrophil chemoattractant-1 [5]. However, there is limited knowledge about the histopathologic events caused by aspiration of AC and PEG solutions. Previous studies have demonstrated that aspiration of gastrointestinal decontamination agents brought about increased microvascular permeability, pulmonary edema, and acute respiratory distress syndrome [7,8]. It is important to clarify the histopathologic mechanisms of acute lung injury caused by aspiration of AC and PEG solutions to develop an effective therapeutic strategy. However, biochemical and histologic changes in the lung tissue if AC and PEG solutions are aspirated are still unclear.

Curcumin (CUR), an active component of the turmeric root (*Curcuma longa*), is known to be an anti-inflammatory, antioxidant, anticancer, and antibacterial agent [9]. Curcumin inhibits the production of TNF-α and IL-1 and reduces the activation of nuclear factor κB and activator protein-1 [10]. Recently, CUR was shown to attenuate acute lung injury, probably through improving oxidative stress levels and inhibiting expression of inflammatory cytokines [10-12]. To date, however, no further histopathologic and biochemical results on lung injury caused by gastrointestinal decontamination agents in rats by CUR treatment have been reported. This study investigates further the potential preventive effect of CUR on lung injury resulting from aspiration of gastrointestinal decontamination agents.

1. Materials and methods

Permission for the study was obtained from the Local Ethics Committee of Animal Testing at Ondokuz Mayis University, Samsun, Turkey; the study was performed at the Ondokuz Mayis University Research and Application Centre of Laboratory Animals.

1.1. Experimental animals and study groups

Forty-two Sprague-Dawley female rats weighing approximately 250 to 300 g were used in our study. The temperature of the environment where the animals' were housed was 20°C to 22°C. The animals were kept in individual cages in a lighted environment for 12 hours and in a dark environment for 12 hours daily and fed with water and food ad libitum. The rats were checked on a daily basis.

The rats were divided randomly into 6 groups (n = 7):

- The animals in group I were the control group. These animals were aspirated intratracheally with 1 mL/kg of 0.9% sterile saline.
- The animals in group II were also aspirated intratracheally with 1 mL/kg of 0.9% saline; after aspiration, these animals were administered 150 mg/kg of CUR (Sigma-Aldrich, St Louis, MO) intraperitoneally (i.p.) once a day for 7 days.
- The animals in group III were aspirated intratracheally with 1 mL/kg of PEG (Paddock Laboratories, Inc, USA).
- The animals in group IV were aspirated intratracheally with 1 mL/kg of PEG; after aspiration, they were administered 150 mg/kg of CUR i.p. once a day for 7 days.
- The animals in group V were aspirated intratracheally with 1 mL/kg of AC (Char-Flo-Aqua Suspension, 206 mg/240 mL; SSM, Chemicalskey, England).
- The animals in group VI were aspirated intratracheally with 1 mL/kg of AC; after aspiration, they were administered 150 mg/kg of CUR i.p. once a day for 7 days.

1.2. Surgical procedure

Before the rats were given intratracheal solutions, they were anesthetized using ketamine hydrochloride (100 mg/kg) and xylazine (10 mg/kg). The animals were positioned supine, and

an anterior neck incision provided tracheal exposure. The materials specified in the description of the groups were injected into the trachea using a 20-gaude needle on a 1-mL tuberculin syringe. The skin incision then was closed using 6-0 Ethilon suture.

Starting the first postperative day, animals in groups II, IV, and VI were injected i.p. with CUR daily for 7 days. After the last CUR injections, all the rats were humanely killed by an i.p. injection of a sufficient dose of ketamine hydrochloride, and both lungs were removed. Portions of the right lung (the anterior lobe, the median lobe, the posterior lobe, and the postcaval lobe) and the left lung (the upper left lobe and the lower left lobe) were evaluated. Each lung lobe section was flattened out in preparation for the histopathologic, immunohistochemical, and biochemical procedures. Histopathologic and immunohistochemical analyses were performed in at least 8 areas of each lung section. The final score in each category for each individual animal was the average of the scores from examining all sections of its lungs.

1.3. Biochemical procedure

1.3.1. Collection of samples

The animals were humanely killed at the end of day 7. The lungs of the animals were studied grossly, and the samples were taken from all lobes of the right and left lungs for both histopathologic and immunohistochemical examination. The lung tissue samples were kept in 10% formaldehyde until the necessary examinations were performed.

Blood samples from the animals that were killed were placed into noncoagulant tubes for biochemical studies. The blood samples in the tubes were centrifuged at 1000 × *g* for 10 minutes within 2 hours after acquisition; the resulting serum samples were kept at −80 °C until they were studied.

1.3.2. Rat pulmonary surfactant-associated protein D

Surfactant-associated protein D (SP-D) derived from the serum samples was studied using an enzyme-linked immunosorbent assay (ELISA) following the manufacturer's instructions (CSB-E12632r, Rat pulmonary SP-D ELİSA kit; Cusabio, China). The color generated was read on a microplate reader at 450 nm, and the results were presented in nanograms per milliliter.

1.3.3. Glutathione peroxidase

The activity of glutathione peroxidase (GSH-Px) in the serum was studied using ELISA following the manufacturer's instructions (ELISA kit; Cayman Chemicals and Pierce Biotechnology, USA). The conversion of NADPH + H^+ into $NADP^+$ was observed as a decrease in absorbance at the 340-nm wavelength. The results of GSH-Px activity were presented in nanomoles per minute per milliliter.

1.3.4. Total superoxide dismutase

The total superoxide dismutase (SOD) activity (Cu/Zn, Mn, and Fe SOD) is observed in our study. Total SOD activity in the serum was studied in accordance with the manufacturer's company's instructions (ELISA kit; Cayman Chemicals Company). *One unit of SOD* was defined to be the amount of enzyme ensuring dismutation of 50% of the superoxide radicals. The results were presented in units per milliliter.

1.3.5. Malondialdehyde

Malondialdehyde (MDA) was studied using the method described by Draper et al [12]. Malondialdehyde values were calculated using the extinction coefficient of the complex of thiobarbituric acid–MDA (1.56×10^5 cm^{-1} $[mol/L]^{-1}$). The results were presented in micromoles per deciliter.

1.4. Histopathologic examination

Specimens taken from each lobe of both lungs were fixed immediately in 10% neutral-buffered formalin and embedded in paraffin wax. Next, the specimens were sectioned (5 μm), and microslides were stained with hematoxylin and eosin for histopathologic assessment under a light microscope by a pathologist blind to the aspirated solution.

Histopathologic examination looked for the peribronchial inflammatory cell infiltration (PICI), alveolar septal infiltration (ASI), alveolar edema (AED), alveolar exudate (AEX), alveolar histiocytes (AHIs), interstitial fibrosis (IF), granuloma (GRA), and necrosis (NEC) formation. All histopathologic findings were evaluated using a scoring system developed by Takıl et al [13] (Table 1). All slides were scored from 0 to 3 according to the degree of histopathologic findings.

1.5. Immunohistochemical examination

Sections perpendicular to the lobar bronchioles were taken from each lobe of both lungs and fixed immediately in 10% neutral-buffered formalin. The fixed tissues were dehydrated in ethanol, cleared in xylene, and embedded in paraffin blocks. Five-micrometer sections were cut and mounted on 3-aminopropyltriethoxysilane–coated slides (Sigma, St Louis, MO). Tissue sections were deparaffinized and rehydrated with distilled water. The microslides were stained using the streptavidin-biotin-peroxidase complex technique (Histostain Plus Kit; Zymed, USA). Endogenous peroxidase was blocked with 3% H_2O_2 for 5 minutes. Slides were then placed in antigen retrieval solution (sodium citrate, pH 6) and heated by microwave oven to room temperature. Next, the tissues were incubated with protein blocking solution for 10 minutes at room temperature. Immediately afterward, the tissues were incubated with the primary antibody for 30 minutes at room temperature.

Anti–TNF-α antibody (1:50; Endogen, IL, USA) and anti–IL-1β (1:100; Endogen, IL, USA) were used as the primary antibodies. For negative control, the primary antibody was evaluated by substituting phosphate-buffered saline for the primary antibody.

All slides were incubated with the secondary antibody, and the horseradish peroxidase–streptavidin solution, respectively, for 30 minutes at room temperature. The slides were stained

Table 1 The 4-point scale used for histopathologic evaluation

	0	1	2	3
PICI	No	Prominent germinal centers of lymphoid follicles	Infiltration between lymphoid follicles	Confluent bandlike form
ASI	No	Minimal	Moderate	Severe, impending of lumen
AED	No	Focal	In multiple alveoli	Widespread, involving lobules
AEX	No	Focal	In multiple alveoli	Prominent, widespread
AHI	No	Scattered in a few alveoli	Forming clusters in alveolar spaces	Filling the alveolar spaces
IF	No	Focal, minimal	Focal, prominent fibrous thickening	Widespread, prominent fibrous thickening
GRA	No	Rare, micro	Focal, well formed	Confluent, large
NEC	No	Focal, few necrotic cells	Multifocal, small areas	Larger areas

with amino ethylcarbazole chromogen and counterstained with Gills hematoxylin. After each step was completed, the slides were washed twice with phosphate-buffered saline solution for 5 minutes, except the protein-blocking step.

The number of TNF-α– and IL-1β–positive cells was assessed using a microscopy image analysis system (Bs200Pro Image analysis system, BAB software, Ankara, Turkey). The number of TNF-α– and IL-1β–positive cells was scored by counting 1000 cells in randomly selected ×10 high-power magnification fields per lung sample. Every stained cell was considered positive regardless of the intensity of the staining. The number of immunopositive cells was recorded as follows: weak, less than 5% (−/+); mild, 6% to 25% (+); moderate, 26% to 50% (++), and strong, more than 50% (+++).

1.6. Statistical methods

All biochemical findings are presented as means ± SD, and the histopathologic scores are presented as median. All findings were developed using SPSS statistical software (SPSS for Windows, version 15.0; SPSS, Chicago, IL). Nonparametric values were analyzed with the Mann-Whitney *U* test. The degrees of histopathologic scores were analyzed using the analysis of variance followed by the Bonferroni post hoc test for detection of significant differences between groups. A *P* value less than .05 was regarded as statistically significant.

2. Results

2.1. Biochemical findings

The measurements of serum surfactant protein D, MDA, SOD, and GSH-Px levels and the statistical significance of these measurements are shown in Fig. 1.

Aspiration of gastrointestinal decontamination agents (AC and PEG) increased the levels of serum surfactant

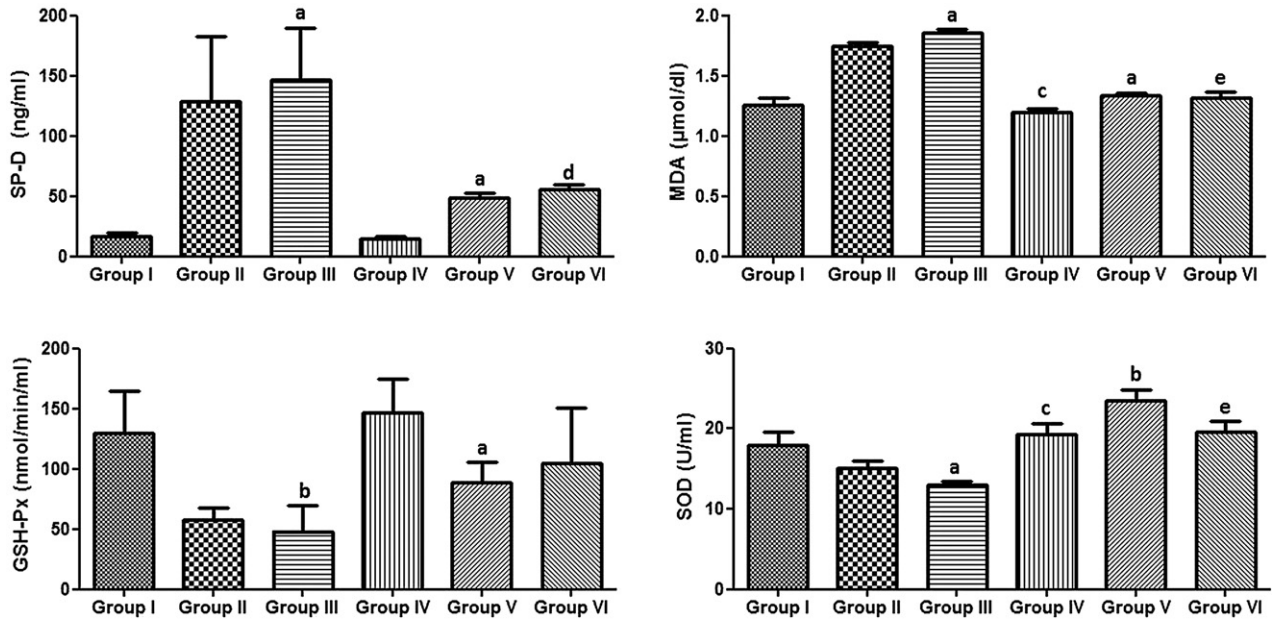

Fig. 1 The effects of CUR treatment on serum SP-D, SOD, MDA, and GSH-Px levels in each groups (n = 7). a, $P < .01$ compared with group I. b, $P < .05$ compared with group I. c, $P < .01$ compared with group III. d, $P < .05$ compared with group V. e, $P < .01$ compared with group V.

Table 2 Histopathologic scores of pulmonary tissue for each group (n = 7)

	Group III	Group IV	Group V	Group VI
PICI	2.14 ± 0.34	0.57 ± 0.20 **	2.00 ± 0.37	0.71 ± 0.18 **
ASI	1.85 ± 0.34	0.42 ± 0.42 **	2.14 ± 0.34	0.71 ± 0.18 **
AED	0.85 ± 0.14	0.71 ± 0.18	1.57 ± 0.20	0.42 ± 0.20 **
AEX	1.71 ± 0.18	0.14 ± 0.14 ***	0.85 ± 0.14	0.57 ± 0.20
AHI	1.14 ± 0.14	0.71 ± 0.18	2.00 ± 0.21	0.28 ± 0.18 **
IF	0.71 ± 0.18	0.28 ± 0.18	0.85 ± 0.14	0.14 ± 0.14 **
GRA	0.85 ± 0.14	0.42 ± 0.42 *	0.28 ± 0.18	0 ± 0
NEC	0 ± 0	0 ± 0	0.85 ± 0.14	0.14 ± 0.14 **

Values are expressed as mean ± SE. Group III, PEG-aspirated group; group IV, PEG-aspirated group treated with CUR; group V, AC-aspirated group; group VI, AC-aspirated group treated with CUR.

* $P < .05$ compared with untreated groups.

** $P < .01$ compared with untreated groups.

*** $P < .001$ compared with untreated groups.

protein D and MDA and decreased the levels of serum antioxidant enzymes SOD and GSH-Px (Fig. 1). Curcumin treatment significantly decreased the elevated serum surfactant protein D and MDA levels and increased the reduced SOD and GSH-Px levels in the sera (Fig. 1).

2.2. Histopathologic findings

The histopathologic scores of PICI, ASI, AED, AEX, AHI, IF, GRA, and NEC in each study group and their statistical significances are shown in Table 2. In this study, the saline groups (groups I and II) showed no obvious changes (Table 2). No IF, GRA, or NEC was observed in these 2 groups. In addition, no NEC was detected in the PEG-aspiration groups (groups III and IV).

According to the scoring system of Takıl et al [13] (Table 1), the alveolar damage in the gastrointestinal decontamination-aspiration groups (groups III and V) was found to have increased, compared with the control saline-aspiration group (group I) (Table 2). Treatment with CUR greatly reduced the morphologic alterations associated with aspiration of gastrointestinal decontamination agents and protecting the alveolar structure (Table 2).

Table 3 Semiquantitative comparison of the positive immunostaining for iNOS, IL-1β, and TNF-α in lung tissues for each group (n = 7)

	Group I	Group II	Group III	Group IV	Group V	Group VI
IL-1β	+	±	++	+	+++	+
TNF-α	+	±	+++	±	+++	+

Group I, saline-aspirated group; group II, saline-aspirated group treated with CUR; group III, PEG-aspirated group; group IV, PEG-aspirated group treated with CUR; group V; AC-aspirated group; group VI, AC-aspirated group treated with CUR.

2.3. Immunohistochemical findings

The immunopositive cell numbers of TNF-α and IL-1β were semiquantitatively higher in groups III and V than in control group I (Table 3; Fig. 2). The immunopositive cell numbers of TNF-α and IL-1β decreased significantly in all treatment groups (Table 3).

The IL-1β immunostaining of lung specimens was significantly higher in groups III and V (median, 2+ and 3+, respectively) than in the control group I (median, 1+) ($P < .05$ and $P < .01$, respectively) (Table 3; Fig. 2). After CUR treatment, the IL-1β immunostaining of lung specimens decreased significantly in group II (median, ±), group IV (median, 1+), and group VI (median, 1+) in contrast to the control group I (median, 1+), group III (median, 2+), and group V (median, 3+) ($P > .05$, $P < .05$, and $P < .01$, respectively) (Table 3).

The TNF-α immunostaining of lung specimens was significantly higher in groups III and V (medians, 3+ and 3+, respectively) than in the control group I (median, 1+) ($P < .01$ and $P < .01$, respectively) (Table 3). After CUR treatment, the TNF-α immunostaining of lung specimens decreased significantly in group II (median, ±), group IV (median, ±), and group VI (median, 1+) in contrast to the control group I (median, 1+), group III (median, 3+), and group V (median, 3+) ($P > .05$, $P < .001$, and $P < .01$, respectively) (Table 3).

3. Discussion

We have demonstrated in this study that CUR, an anti-inflammatory, antioxidant, and antibacterial agent, prevents lung damage caused by aspiration of AC and PEG solutions. Curcumin attenuated lung parenchymal destruction and inflammatory infiltration induced by aspirating AC and PEG solutions by decreasing the serum MDA and surfactant protein D levels, increasing the antioxidant enzyme levels, and inhibiting the expressions of TNF-α and IL-1β in lung tissue. Our findings indicate that CUR can prevent lung injury induced by gastrointestinal decontamination agents.

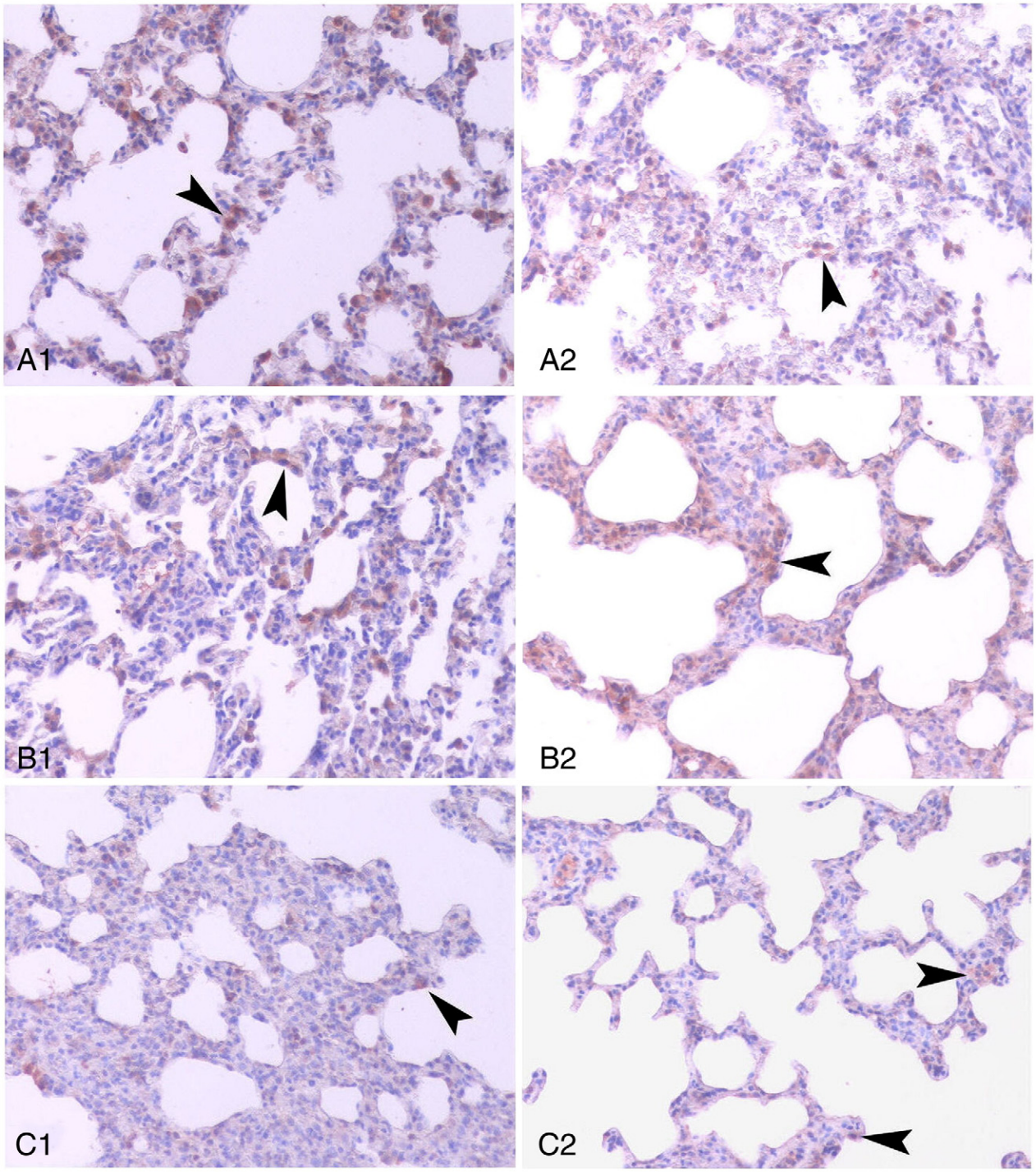

Fig. 2 Immunohistochemical expressions of IL-1β and TNF-α in all study groups (n = 7). IL-1β (A1); group V, strong immunopositive reaction of IL-1β and immunopositive cells seen in interalveolar septal tissue (arrowhead). B1, Strong immunopositive reaction of IL-1β in interalveolar septal tissue and alveolar type II cells (arrowhead) in group III. C1, Weak immunopositive reaction of IL-1β (arrowhead) and moderate inflammatory reaction in interalveolar tissue in group I. TNF-α (A2), strong immunopositive reaction of TNF-α and immunopositive cells seen in interalveolar septal tissue (arrowhead) in group V. B2, Strong immunopositive reaction of TNF-α in interalveolar septal tissue (arrowhead) and moderate inflammatory reaction in group III. C2, Weak immunopositive reaction of TNF-α (arrowhead) and moderate inflammatory reaction in interalveolar tissue in group I. Immunoperoxidase technique, Harris hematoxylin counter staining, amino ethylcarbazole as a chromogen, ×20.

Administration of AC and PEG solutions is a gastrointestinal decontamination procedure commonly used in treating these poisoning patients. The most common complication associated with gastrointestinal decontamination is aspiration that results from a combination of the patient's depressed mental status, loss of protective airway

reflexes, spontaneous or drug-induced emesis, and manipulation of the respiratory tract and gastroesophageal area [14,15]. Some authors reported that the incidence of aspiration after gastrointestinal decontamination is approximately 2% [16]. Aspiration of gastrointestinal decontamination agents gives rise to acute pneumonitis, pulmonary edema, bronchiolitis obliterans, acute respiratory distress syndrome, obstruction of the airway, pleural effusion, pneumothorax, and bronchopleural fistula [17-19].

There are a few reports of AC and PEG aspiration–induced lung injury in the literature [3-5,20-22], but the histopathologic and molecular mechanisms of lung injury induced by aspirating gastrointestinal decontamination agents are still unclear. Some authors showed that alveolar atelectasis, granulomatous reaction, peribronchial infiltration, and septal inflammation existed in lung tissue after aspiration of these agents [23]. Our histopathologic findings were consistent with the results of previous studies. All histopathologic measures deteriorated after aspiration of AC and PEG by rats. These findings were ameliorated in all groups treated with CUR.

Several biomarkers and inflammatory mediators have been studied in aspiration and pneumonia [5,6,22]. These biomarkers have been found to guide the diagnostic and therapeutic approaches in pneumonia. The role of these biomarkers in the management of aspiration syndromes has been inconclusive. Experimental studies have reported that lung injuries induced by aspirating gastrointestinal contents are associated with an increased expression of inducible nitrous oxide synthase, elevated serum surfactant protein levels, increased TNF-α and IL-1β levels on bronchoalveolar lavage, collection of lipid peroxidation markers such as MDA, decreased antioxidants such as SOD and GSH-Px, and increased inflammatory mediators [9,22,24-27]. Our findings showed that serum MDA levels and the expression of TNF-α and IL-1β in alveolar epithelial cells were up-regulated after lung injury induced by aspirating AC and PEG solutions and down-regulated remarkably after CUR treatment. In addition, another hallmark of lung injuries induced by aspiration of AC and PEG solutions, as well as depressed levels of serum SOD and GSH-Px, were up-regulated after CUR administration. We also observed an increment of histopathologic findings in alveolar epithelial cells; however, the administration of CUR significantly reduced the expression of TNF-α and IL-1β in alveolar epithelial cells.

Surfactant protein D, a member of the collectin family, is a large oligomeric protein produced by alveolar type II cells [28]. The main role of surfactant protein D is to decrease alveolar surface tension, preventing collapse at the expiratory phase of respiration and vascular-to-alveolar permeability [29]. In addition, surfactant protein D modulates the cellular immune response [32] and has a direct effect on microbacterial activation [30-33]. Lipid peroxidation initiated by oxygen radicals and damage of surfactant protein structure may contribute to the impaired functions of alveolar type II cells and NEC associated with aspiration of gastrointestinal contents [30,34]. However, increased serum surfactant protein D levels are indicative of alveolar damage because surfactant protein D is found almost exclusively within alveolar type II cells in lung tissue [35]. The increased microvascular permeability caused by alveoloepithelial injury to lungs from aspirating gastrointestinal content brings about increased serum surfactant protein D levels. We found higher serum surfactant protein D levels in the AC- and PEG-aspiration groups as compared with the control in our study. We thought that the increased levels of serum surfactant protein D showed degrees of alveolar damage. Administering CUR significantly decreased the serum surfactant protein D levels in the treatment groups compared with the untreated groups.

Turmeric has been applied as ayurvedic medicine since ancient times [36]. Although a few studies on the possible medicinal applications have been done, no clinical studies for drug development have been put into practice as yet [37]. Curcumin is a biologically active phytochemical substance present in turmeric that represents a wide spectrum of biological effects and is nontoxic; it would be easier to develop new drugs from this form after extensive studies on its mechanism of action and pharmacologic effects [36]. Some clinical studies about effectiveness of CUR on different inflammatory diseases including rheumatoid arthritis, inflammatory eye diseases, inflammatory bowel disease, chronic pancreatitis, psoriasis, hyperlipidemia, and cancers have been done [37,38]. All findings to date are preliminary and not conclusive. It is expected that CUR may find application as a novel drug in the near future to control inflammatory disorders and oxidative stress–induced pathogenesis.

4. Conclusion

Although previous experimental studies have used several antioxidant and anti-inflammatory drugs to treat lung injury caused by aspiration, there have been no studies evaluating the role of CUR in treating lung injury caused by aspiration of gastrointestinal decontamination agents. To the best of our knowledge, our findings provide the first study evaluating the effect of CUR in the pathogenic process of lung injury induced by aspiration of gastrointestinal decontamination agents. Our results show that CUR has a preventive effect on this condition. As a result, we believe that CUR may be a potentially useful therapeutic drug for this type of lung injury. However, well-designed clinical studies, supported by better formulations of CUR or novel routes of administration, are required to validate our findings.

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