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Original article

Effect of N-acetyl-cysteine nanoparticles on intra-abdominal adhesion after laparotomy in rats

Sh. Shahzamani[1], AR. Jahandideh[1], GhR. Abedi[1], A. Akbarzadeh[2, 4], S. Hesaraki[3]

[1] Department of Clinical Science, Faculty of Specialized Veterinary Sciences, Science and Research Branch, Islamic Azad University, Tehran, Iran
[2] Universal Scientific Education and Research Network (USERN), Tabriz, Iran
[3] Department of Pathobiology, Faculty of Specialized Veterinary Sciences, Science and Research Branch, Islamic Azad University, Tehran, Iran
[4] Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

Abstract

Postoperative adhesion (POA) is a common and well-known complication with an estimated risk of 50-100%. The antioxidant effect of n-acetyl-cysteine (NAC) can increase intracellular glutathione levels, thereby reducing adhesion. This study was conducted to compare the outcomes of NAC nanoparticles (Nano-NAC) on intra-abdominal adhesion (IAA) after laparotomy in rat.

A total of 25 male Wistar rats were randomized into five groups: 50 mg/kg Nano-NAC, 75 mg/kg Nano-NAC, 150 mg/kg Nano-NAC, NAC and control. During the surgical procedure, some sections (2×2cm) were collected through abdominal midline incision to ensure the infliction of peritoneal damage by a standard adhesion. Macroscopic evaluation was performed on the 14th and 28th day and blood samples were collected to evaluate the inflammatory factor (C-reactive protein) on days 0, 14 and 28. According to the serologic results (CRP test), C-reactive protein was at highest level in 150 mg/kg Nano-NAC and control groups and at lowest level in 50 mg/kg Nano-NAC and 75 mg/kg Nano-NAC groups ($p<0.001$). The macroscopic evaluation results showed that frequency of adhesion bands was significantly lower in 50 mg/kg Nano-NAC group than the control at the intervals. Results showed that the intraperitoneal administration of lower Nano-NAC dosages (50 and 75 mg/kg) had a major role in the management of postoperative inflammation. Nano-NAC administration was proved feasible, safe and effective in reduction of the C-reactive protein level.

Key words: N-acetyl-cysteine nanoparticles, intra-abdominal adhesion, laparotomy, rat

Correspondence to: A. Jahandideh, e-mail: dr.jahandideh@gmail.com

Introduction

Adhesions caused by abdominal surgery are a very common and complicated problem with the incidence rate of over 50%. For example, post-surgical problems caused by pelvic-abdominal adhesions include infertility, small bowel obstruction, and chronic pelvic problems difficulty of subsequent access to which during surgery increases the mortality associated with surgeries performed in the area (Amribaigloo et al. 2018).

Postoperative adhesion is defined as pathologic bands between surfaces of peritoneal or pelvic cavities formed by peritoneal surface defects or peritoneal scarring. Different etiological factors have been reported for postoperative adhesion, such as infection, intestinal fistulas, ischemia at suture sites, foreign bodies, and mechanical trauma from tissue handling and retractors (Schnüriger et al. 2011). The treatment of postoperative adhesion complications increases medical costs and reduces the quality of life due to frequent hospitalization and various adhesion treatment procedures, such as adhesiolysis, with estimated direct cost of $1.33 billion (Tabibian et al. 2017). To prevent the formation of adhesion bands following surgery, numerous materials have been studied, including glucocorticoids, heparin, dextran 70, normal saline, antibiotics, promethazine, antihistamines, prostaglandin synthesis inhibitor, Lactated Ringer's solution, calcium channel inhibitors, streptokinase as a fibrinolytic agent, rofecoxib as the inhibitor of cyclooxygenase, methyl blue, and octreotide (Li et al. 2014).

NAC is a clinical antioxidant used for the treatment of numerous disorders in patients aged over 50. These disorders include oxidative stress, ranging from preventing ischemic reperfusion injuries to regulate tumorigenesis, presumably due to its proved effects on important cellular pathways such as inflammation, oxidative stress, and angiogenesis (Bulut et al. 2015, Xue et al. 2015). Moreover, NAC is used as mucolytic to dissipate disulfide bonds across mucoproteins, as antioxidant agents, and to reduce hydroxyl radical (OH), hydrogen peroxide (H_2O_2) and superoxide (O_2^{2-}), and as inducer of glutathione (GSH) (Kabali et al. 2009). To the best of our knowledge, there are scant prospective studies that have evaluated the effect of NAC, specifically Nano-NAC, on intra-abdominal adhesion; therefore, we hypothesized that NAC can decrease intra-abdominal adhesions because of its antioxidant properties. Nanoparticles are very fine particles with a diameter less than 100 nm. Due to this property, their activity dramatically increases (Rivas et al. 2017). This study for the first time used Nano technology and production of Nano-NAC to investigate the effect of using Nano-NAC on intra-abdominal adhesion after laparotomy in rat from serologic and macroscopic perspectives.

Materials and Methods

Subjects and Surgery

This study was conducted after obtaining the approval from the Ethics Committee of Islamic Azad University, Sciences and Research Branch, Tehran. It was designed in a way to use the minimum number of animals for examination (only 25 rats).

Experimental animals

A total of 25 adult male albino Wistar rates (weight range: 200-250 grams; age: 4 months) were transferred to the laboratory animal storage facility and maintained according to the animal welfare and ethical norms. Two weeks before laparotomy, the rats were transferred to a room to get used to their new environment and minimize the mortality rate. The animals had no history of undergoing surgery or any other medical intervention. The housing conditions were cages with a normal temperature (20-22°C), each containing 5 rats, and 12 hours of daylight and 12 hours of darkness. They were fed with a standard pellet and water ad libitum. In addition, no special vaccine or anti-parasitic drug was used during this period.

Surgical Procedures

All animals underwent a standard operation conducted similarly by one person. Anesthesia was induced in all groups through intramuscular (IM) injection of ketamine 10% (dosage: 20mg/kg) and IM injection of xylazine 2% (dosage: 2mg/kg). After shaving the surgery site, 10% povidone-iodine was applied the surgical site in the midline region of the abdomen using. The surgical incision, measuring 3 cm in length, was made in the abdomen midline. After entering the abdominal cavity, three incisions, measuring 2 cm in length, were made longitudinally and transversely on the right wall of abdomen using scalpel (No. 24). On the left side of the abdominal wall, some samples (2×2cm) were collected with surgical scissor from the peritoneal surface (Parsaei et al. 2013). These techniques were used to ensure that a standard adhesion with peritoneal damage was formed by removing the peritoneal surface from the internal surface of the peritoneum and destroying the wall with scalpel blade. Then, the surgical wound was sutured with a 0.3 (USP) absorbable delicate filament, adjacent sutures were 1 cm apart (4 sutures), according to their absorbable properties. We did not consider the suture as a foreign body in the abdominal cavity and avoided peritoneal stimulation to form adhesions, and tried to remain the adhesion levels unchanged in all rats.

Table 1. Severity of fibrosis, inflammation, and adhesion.

Grade	Severity of fibrosis	Severity of inflammation	Adhesion
0	no fibrosis	no inflammation	No adhesion
I	low	Giant Cells, Lymphocytes and Plasma Cells	A narrow, adhesive band without a vessel and easily detachable
II	medium	Giant Cells, Plasma Cells, Eosinophils and Neutrophils	Two non-vascular adhesive bands and easily detachable
III	high	Infiltration of inflammatory cells and micro-abscess	Three non-vascular adhesive bands and easily detachable
IV	-	-	More than 3 adhesive bands without vessels and are easily detachable or diffuse adhesion

Table 2. Analysis of C-reactive protein concentration in all groups before and after intervention.

Group Variables		Nano-NAC			NAC	Control	P-value
		150 mg/kg	75 mg/kg	50 mg/kg			
CRP (mg/L)	Before LP	43.82 ± 0.19	43.96 ± 1.16	43.8 ± 0.24	43.5 ± 0.92	43.9 ± 0.45	P1: 0.56 P2: 0.688 P3: 0.577 P4: 0.925
	Day 14	51.84 ± 0.84	38.22 ± 0.57	37.28 ± 0.46	42.52 ± 1.83	50.1 ± 3.73	P1: <0.001 P2: <0.001 P3: <0.001 P4: <0.001
	Day 28	40.98 ± 1.33	38.08 ± 0.57	37.1 ± 0.71	38.4 ± 1.22	42.16 ± 0.35	P1: <0.001 P2: <0.001 P3: <0.001 P4: <0.001

P1: Between Nano-NAC 150 mg/kg, NAC and controlP2: Between Nano-NAC 75 mg/kg, NAC and control
P3: Between Nano-NAC 50 mg/kg, NAC and control
P4: Between Nano-NAC 150 mg/kg, 75 mg/kg, 50 mg/kg

The non-intraabdominal muscle-fascia-skin specimens was sutured with 0.2 (USP) non-absorbent filament, adjacent sutures were 1 cm apart (4 sutures). Postoperative care, including analgesic injection, was done using Buprenorphine (dosage: 0.02 mg/kg SC). Then, the skin was disinfected and the rats were kept under appropriate temperature conditions. Skin sutures were removed on the 7th day after the surgery.

Treatment

A total of 25 rats were randomized into five groups: 50 mg/kg Nano-NAC, 75 mg/kg Nano-NAC, 150 mg/kg Nano-NAC, NAC and control. In the intervention groups, Nano-NAC (dosage: 50, 75, 150 mg/kg) and NAC (150 mg/kg) were poured into the abdomen immediately after accessing the abdominal cavity and making incisions. In the control group, immediately after the incision, 2 ml of the sterile physiological serum was poured inside the abdomen. The duration of the treatment was 28 days. All of the rats survived until the last day, i.e. day 28, and no new rats were added to the groups. The days in which the adhesion model was implemented was taken as day 0. In order to carry out macroscopic assessments, the animals underwent two laparotomies, 14 and 28 days after the induction of the adhesion model. To this end, after anesthesia induction, each rat's abdomen was opened and the adhesion rating was determined, and after every laparotomy done under standard and aseptic conditions, the surgical region was sutured. To compare the adhesions, the severity of each one was measured separately based on following scales (Table 1).

In order to perform serologic Test (CRP test), and measure C-reactive protein, blood samples were drawn from the rats on days 0, 14, and 28, after adhesion model induction, for serum separation and CRP testing. CRP is a blood test marker of inflammation in the body which is classified as an acute phase reactant. CRP is produced in the liver and released into the bloodstream in cases of tissue damage, infection or inflammation. The C-Reactive Protein test (CRP) is based on the principle of the latex agglutination (Serology kit).

Table 3. Macroscopic evaluation in all groups before and after intervention.

Group Variables		Nano-NAC			NAC	Control	P-value
		150 mg/kg	75 mg/kg	50 mg/kg			
Macroscopic evaluation	Day 14	0: 3 (60%) I: 2 (40%)	0: 2 (40%) I: 3 (60%)	0: 3 (60%) I: 2 (40%)	0: 1 (20%) I: 3 (60%) II: 1 (20%)	II: 3 (60%) III: 1 (20%) IV: 1 (20%)	P1: 0.087 P2: 0.13 P3: 0.087 P4: 0.765
	Day 28	0: 4 (80%) I: 1 (20%)	0: 4 (80%) I: 1 (20%)	0: 5 (100%)	0: 3 (60%) I: 2 (40%)	0: 2 (40%) I: 2 (40%) II: 1 (20%)	P1: 0.547 P2: 0.547 P3: 0.249 P4: 0.562

P1: Between Nano-NAC 150 mg/kg, NAC and control
P2: Between Nano-NAC 75 mg/kg, NAC and control
P3: Between Nano-NAC 50 mg/kg, NAC and control
P4: Between Nano-NAC 150 mg/kg, 75 mg/kg, 50 mg/kg

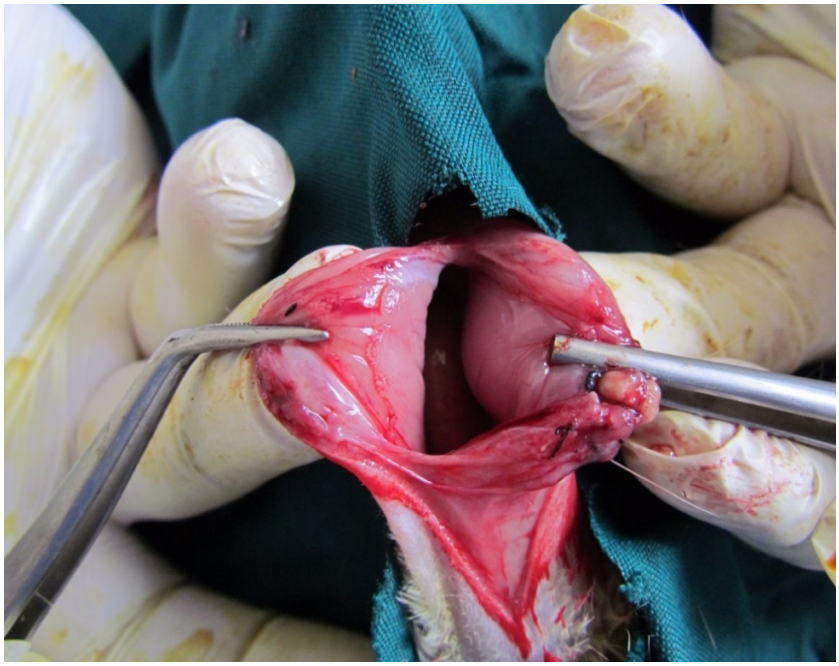

Fig. 1. Zero grade

The values for CRP in all samples and the specified days are presented in Table 2.

Data analysis

Data were analyzed and reported for all rats (25). The statistical data analysis was performed using SPSS22 (SPSS Inc., Chicago, IL, USA). To compare qualitative variables between groups, the Chi-square test was used. The normal distribution of all studied parameters was checked using the Kolmogorov-Smirnov test. The Student t-test and paired t-test were used for normally distributed variables: besides, the Mann-Whitney and Wilcoxon test were used for abnormally distributed variables. In the two tailed test, p-value less than 0.05 was considered significant.

Results

Based on the results from the analysis of blood samples after 14 days, C-reactive protein was at highest level in 150 mg/kg Nano-NAC (51.84 ± 0.84mg/L) and control group (50.1 ± 3.73mg/L), and at the lowest level in 50 mg/kg Nano-NAC (37.28 ± 0.46mg/L) and 75 mg/kg Nano-NAC (38.22 ± 0.57mg/L) ($p<0.001$). Moreover, by comparing different dosage of Nano-NAC, we found C-reactive protein level was lower in 50 mg/kg Nano-NAC group than in other Nano-NAC groups ($p<0.001$). According to Table 2, after 28 days from surgery, we found that the C-reactive protein was at the highest level in the control (42.16 ± 0.35mg/L) and 150 mg/kg Nano-NAC (40.98 ± 1.33mg/L) groups and at the lowest level in 50 mg/kg Nano-NAC (37.1 ± 0.71 mg/L) and 75 mg/kg Nano-NAC

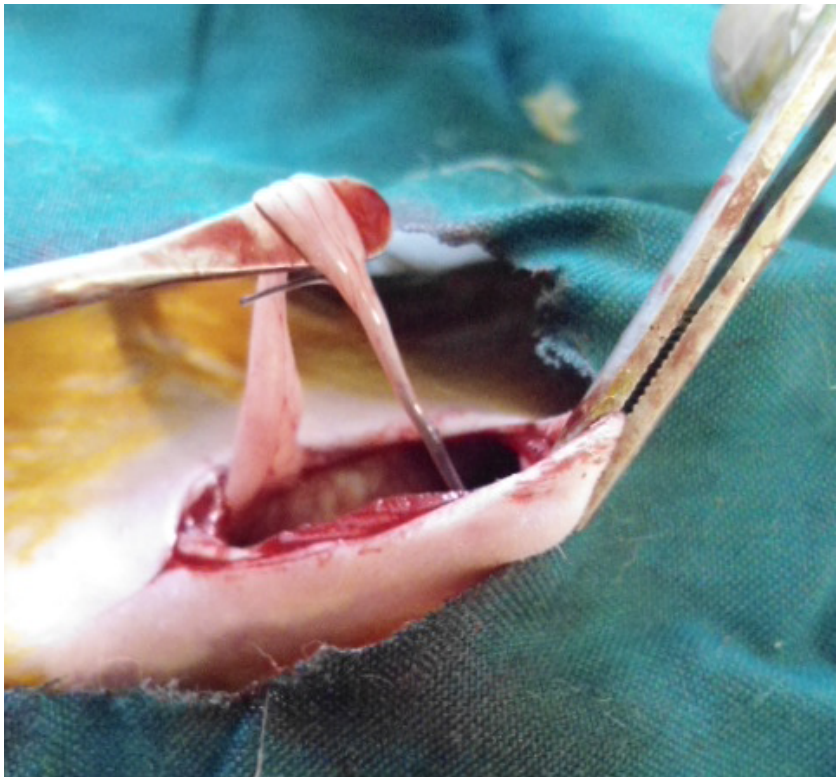

Fig. 2. grade I

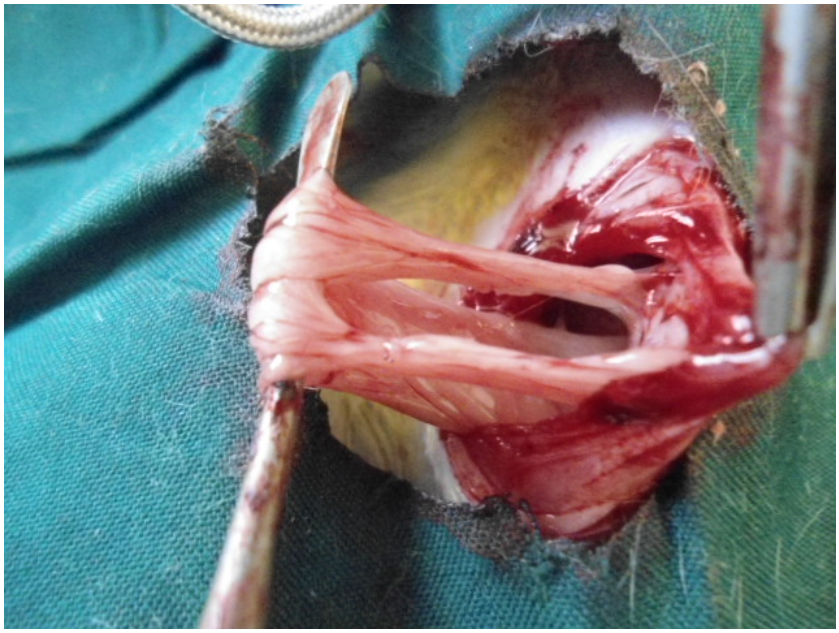

Fig. 3. grade IV

(38.08 ± 0.57 mg/L) groups ($p<0.001$). On the other hand, there was no significant between-group difference in macroscopic results on the 14th and 28th day ($p>0.05$).

In both surgeries for macroscopic evaluation, no sign of ascites and intraabdominal viscous fluid was observed. The frequency of adhesion bands in 50 mg/kg Nano-NAC was significantly lower (3 cases: 60% and 5 cases: 100% with zero scale) (Fig. 1) than in the control group with (3 cases: 60% with scale II and 2 cases: 40% with scale I) (Fig. 2) on the 14th and 28th days (Table 3). The grade IV, as the worst grade, was only seen in one case: 20% on the 14th day in the control group (Fig. 3). Moreover, the frequency of low grades in 50 and 75 mg/kg Nano-NAC groups (in 14 days) was significantly lower (4 cases: 80%

with zero scale for both groups). According to Table 3, this frequency was significantly lower only in 50 mg/kg Nano-NAC group (4 cases: 80% with zero scale) on the 28th day. The grade IV, as the worst grade, was only seen in one case in the control group (20% on the 14th day).

Discussion

Abdominal surgery causes injury to the peritoneum, and activates the surrounding mesothelium and underlying endothelium, resulting in increased level of inflammatory cytokines, such as tumor necrosis factor alpha and interleukin-6, the subsequent increase in neutrophils, macrophages, and eosinophils, in the abdominal cavity and induction of fibrinous exudate into the peritoneum (Cheong et al. 2002). Both processes, i.e. the activation of the mesothelium and underlying endothelial cells, and infiltration and subsequent activation of neutrophils and macrophages, are correlated with significant oxidative stress (Gotloib et al. 2004). Therefore, antioxidant treatments, such as NAC, can also inhibit adhesion formation.

According to the literature, factors that reduce adhesion are divided into two categories. The first group includes substances used directly or systemically in the abdominal area. The second group includes substances used topically (Flessner 2005). Most initial efforts to reduce inflammatory reactions have been based on the use of steroids and NSAID; however, their adverse systemic and topical effects, such as increased bleeding and delayed healing, have limited their application (Mahdy et al. 2008). Another group of substances that are able to reduce adhesion include Hyaluronic acid-carboxymethylcellulose, oxidized regenerated cellulose, Icodextrin 4%, Polytheaphlorothiazide, bioabsorbable gels and fluid agents, such as crystalloid and high molecular weight sugar (Boland et al. 2006). Although, hyaluronic acid solution (0.4%), as one of the most popular substances to reduce adhesion, is nowadays broadly used, it is very costly. In contrast to NAC which has a high permeability effect, hyaluronic acid solution has an anti-adhesion limitation of its own and requires a carrier to act properly (Cashman et al. 2011). Oxidized regenerated cellulose, which is approved by the FDA and is used as a golden standard for reducing abdominal cavity adhesions, is also costly and complex (Dinarvand et al. 2013).

Several fluids (e.g., crystalloid and high molecular weight sugars), gels, or solids are also used to reduce adhesion. Although these substances can well be distributed in abdominal cavity and provide adequate contact with peritoneal surfaces, their adverse effects, such as edema in the perineum and pulmonary area, have been reported following their administration. Fluids used to reduce intraabdominal adhesions are presented by Aslan et al. (2017). In their study, all rats in the group receiving saline solution had adhesion; whereas, none of the rats in NAC group had either severe reaction of inflammatory cell or dense interstitial fibrosis. Moreover, lower macroscopic and microscopic adhesion formation was found in the NAC group. The use of gels has not been approved by clinicians (Ward et al. 2011).

Furthermore, some studies have reported that oxidative stress can decrease fibrinolytic activity. A study conducted by Nielsen et al. (2004) showed that oxidants can directly inactivate tissue plasminogen activator. In another study Kuyumcu et al. (2015) showed that plasma malondialdehyde, glutathione and oxidized glutathione and urinary nitrate level were significantly lower in the NAC group in major abdominal surgery patients than the control group. Moreover, Heydrick et al. (2007) showed that NAC significantly decreased peritoneal oxidative stress by reduction of 8-isoprostane levels in both peritoneal tissue and fluid. These results indicated the beneficial effects of NAC administration on antioxidant parameters in abdominal surgery patients and should be considered as an effective procedure in improving oxidative status and reducing postoperative inflammation and adhesion.

A study conducted by Pourreza et al. (2015) suggested the probable effectiveness of NAC in reducing adhesion in human and veterinary medicine. They reported lower inflammation intensity based on a complete blood count, different fibrinogen concentration, lower fibrosis levels and lower adhesion formation in macroscopic evaluation. Although, we did not find significant changes in macroscopic results, we found lower CRP level in NAC group than the control group. On the other hand, we found that lower dose of Nano-NAC was more effective than NAC alone.

Furthermore, Chu et al. (2011) reported that intraperitoneal administration of NAC decreased postoperative adhesion formation by up-regulation of antioxidant defense and peritoneal fibrinolytic activity without affecting normal anastomotic wound healing.

In conclusion, a single dose of NAC given intraperitoneally can reduce postoperative intraabdominal adhesions (Bulbulogluet al. 2011).

Nano particles have increase surface area, and thus are used for drug delivery. Nano particles have unique biological and chemical properties as compared to their larger counterparts (Nikalje 2015). To the best of our knowledge, this is the first study on Nano-NAC effectiveness in reducing postoperative adhesion as compared to NAC alone.

According to the results, no significant change was observed in macroscopic features of postoperative

adhesion; whereas, a significant reduction was observed in CRP level in group receiving 50 mg/kg Nano-NAC. In general, the administration of 50 mg/kg Nano-NAC can be effective in controlling postoperative adhesion and specifically in reducing C-reactive protein level. However, we did not find any significant change in macroscopic adhesion formation in NAC and Nano-NAC groups, whereas, we found lower CRP postoperatively in Nano-NAC and NAC groups than in the control group.

Conclusions

Results showed that the intraperitoneal administration of lower doses of Nano-NAC (50 and 75 mg/kg) plays a major role in the management of inflammation after surgery. Nano-NAC administration has been proved feasible, safe and effective in reduction the level of CRP. Nano-NAC administration is particularly beneficial in preventing postoperative adhesion, which previously required surgery as nonoperative treatments were more likely to fail.

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