

## Effect of gold nanoparticles on postoperative peritoneal adhesions in rats

<sup>1</sup>A.H. Mohammadpour; <sup>2</sup>A. Tavassoli; <sup>3</sup>M.R. Khakzad; <sup>4</sup>E. Zibae; <sup>5</sup>M. Afshar; <sup>6</sup>M. Hashemzadei; <sup>7\*</sup>Gh. Karimi

<sup>1</sup>Department of Clinical Pharmacy, School of Pharmacy, Pharmaceutical Research Center, Mashhad University of Medical Sciences, Mashhad Iran

<sup>2</sup>Endoscopic & Minimally Invasive Surgery Research Centre, Ghaem hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

<sup>3</sup>Allergy Research Center, Mashhad University of Medical Sciences, Mashhad, Iran, Department of Immunology, Mashhad Branch, Islamic Azad University, Mashhad, Iran

<sup>4</sup>Department of Clinical Pharmacy, School of Pharmacy, Mashhad University of Medical Science, Mashhad, Iran

<sup>5</sup>Department of Anatomy, Faculty of Medicine, Birjand University of Medical Sciences, Birjand, Iran

<sup>6</sup>Department of Pharmacology and Toxicology, School of Pharmacy, Zabol University of Medical Science

<sup>7</sup>Medical Toxicology Research Center, School of Pharmacy, Mashhad University of Medical Science, Mashhad Iran

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### ABSTRACT:

**Objective(s):** Abdominal adhesions are one of the most important problems, occurring after intra-abdominal surgery in more than 90% of cases. This condition is the leading cause of bowel obstruction, infertility, and abdominal/pelvic pain. Gold nanoparticles (GNPs) have been shown to be non-toxic and exhibit anti-inflammatory, anti-angiogenic and antioxidant activities. The purpose of this study was to determine the effect of intraperitoneal lavage with GNP solutions on the development of postoperative peritoneal adhesion (PPA).

**Materials and Methods:** In the current experimental study, thirty-five male Wistar rats were randomly assigned to seven groups of five rats. After a standardized peritoneal injury, GNP solutions in different concentrations (1, 2.5, 5, 10, 50 and 100 ng/ml) were locally administered through nebulization; normal saline (NS) was administered to the control group. Two weeks later, the rats were sacrificed and cecum and peritoneal samples were harvested for histopathological assessment. Blood samples were obtained to determine serum concentrations of inflammatory biomarkers including tumor necrosis factor alpha (TNF- $\alpha$ ), interleukin-1 beta (IL-1 $\beta$ ) and vascular endothelial growth factor (VEGF).

**Results:** The rats treated with GNPs had significantly lower microscopic and macroscopic peritoneal adhesion scores, compared to the control group ( $P < 0.05$ ). Score 5 of macroscopic adhesions was reported in all the rats of the control group, unlike the GNP groups. Furthermore, microscopic adhesions were reported with all rats in the control group, unlike the GNP groups (reported in 0 out of 5 rats in all GNP groups). In addition, serum levels of IL-1 $\beta$ , TNF- $\alpha$  and VEGF underwent no significant changes.

**Conclusion:** Compared to the control group, GNPs decreased the severity of peritoneal adhesions, although they did not alter TNF- $\alpha$ , IL-1 $\beta$  or VEGF serum levels.

**Keywords:** Gold nanoparticles, Nebulization, Postoperative peritoneal adhesion, Rat

### INTRODUCTION

Postoperative peritoneal adhesion (PPA) is a frequent complication after abdominal surgery. In fact, peritoneal injury after abdominopelvic surgery is the most

common cause of abdominal adhesion; less common causes include inflammatory conditions, intra-peritoneal infections, and abdominal trauma [1]. Fibrous bands between organs or tissues (or both) develop soon after surgery (after about three hours) [2]. Abdominal injuries result in the release of inflammatory cytokines including tumor necrosis factor alpha (TNF- $\alpha$ ), interleukin-6 (IL-6) and interleukin-1 beta (IL-1 $\beta$ ) [3, 4].

✉ \*Corresponding Author Email: [karimig@mums.ac.ir](mailto:karimig@mums.ac.ir)  
Tel: (+98) 38823255

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Both TNF $\alpha$ , IL-1 $\beta$  are proinflammatory cytokines that play important roles in the early phases of wound healing process and are produced via activated macrophage in peritoneal fluids [5,7]. Furthermore, increased production of IL-1 $\beta$  by activated macrophage induces IL-6 expression [8]. Expression of inducible cyclooxygenase (COX2), as an activated enzyme, leads to increasing levels of inflammatory mediators such as thromboxane, interleukins and prostaglandins [8]. TNF $\alpha$  plays an important role in adhesion band formation [7, 9]. Recruitment of neutrophils, macrophages and eosinophils leads to the release of fibrinous exudates at the abdominal cavity [2]. Vascular endothelial growth factor (VEGF) is another signal protein, which plays a critical role in the vasculogenesis and angiogenic process [10]. Many previous studies showed that VEGF antibodies reduced the formation of adhesion bands [11-13]. Moreover, significant oxidative stress is induced by the activation of mesothelium and endothelial cells along with the infiltration and activation of neutrophils and macrophages. Ultimately, this inflammatory process leads to the formation of nascent fibrinous adhesions and expands to fibrins [4]. Although the application of new surgical techniques such as laparoscopy is expanding, it is not always possible or appropriate to perform all types of surgical interventions for patients. PPA occurs in 93-100% of patients who undergo trans-peritoneal surgery. This condition can induce bowel obstruction, infertility, abdominal pain, pelvic pain, and difficulties during the new surgical interventions [9, 11, 14, 15]. Gold in its natural state is a non-toxic compound for humans and is used extensively in cancer diagnosis and treatment. Considering the established use of gold in laboratory and the chemical stability of gold, gold nanoparticles (GNPs) are expected to be harmless [16, 17]. GNP have been shown to exhibit anti-inflammatory, immunomodulatory, and antioxidant activities and possess anti-angiogenic, analgesic, and restorative effects [8, 18, 19]. In addition, GNPs are widely used in biomedical imaging and diagnostic tests [20]. GNPs pose anti-angiogenic effects via targeting multiple pro-angiogenic cytokines, which contain heparin-binding domains including VEGF and basic fibroblast growth factor. VEGF has been shown to have wound-healing effects [19]. Given the role of angiogenesis in peritoneal adhesion, this process may be useful for adhesion prevention. Moreover, GNPs decrease TNF $\alpha$ , IL-1 $\beta$  levels in synovial fluids of animals with rheumatoid

arthritis [21]. Auranofin, a gold-containing sulfur, exhibits antioxidant effects by subsiding cytokine production including IL-6 and IL-1 $\beta$  [8]. IL-6 induces VEGF gene expression, which play a pivotal role in the angiogenesis and is involved in postoperative peritoneal adhesion [8]. The current study is the first to investigate the effects of intra-peritoneal lavage with GNPs on the development of PPA in Wistar rats.

## MATERIALS AND METHODS

### Materials

GNPs (300 nm in size) were purchased from Sigma-Aldrich (USA) with more than 95% spherical particles. TNF $\alpha$ , IL-1 $\beta$  and rat VEGF ELISA kits were purchased from RayBiotech Co. (USA).

### Animals

Adult male Wistar rats (weighing 250-300 g) were obtained from the School of Pharmacy of Mashhad University of Medical Sciences. Animals were allocated into groups of five and housed in cages; animals were given food and water ad libitum and kept on a 12-h light/12-h dark cycle. All methods used in this study were in accordance with the guidelines by the declaration of Helsinki for experimental studies on animals [22].

### Surgical procedure

Animals were subjected to anesthesia, using an intra-peritoneal (IP) injection of ketamine 100 mg/kg and xylazine 10 mg/kg. The abdomen was then shaved and prepared with alcohol and iodine solution. After drying, 3 cm laparotomy was performed to gain access to the abdominal cavity. To form an adhesion, Peritoneal Button Creation (PBC) technique was applied, which is considered the most consistent and reproducible animal technique for the intra-abdominal adhesion model [1]. Barbed 2.0 polypropylene sutures in a chain distribution were used on the parietal peritoneum to create four peritoneal buttons. Each suture encapsulated approximately 2 cm of parietal peritoneum; the diameter of the tied sutures were approximately 5 mm. Different concentrations of GNPs were locally administered in the peritoneal cavity via nebulization and then the peritoneum was sutured. Two weeks later, animals underwent a laparotomy and cecum and peritoneal samples were sent for histopathological examinations; adhesion formation intensity was recorded according to the Adhesion Scoring System (ASS). Blood samples were obtained to determine

the serum concentrations of inflammatory biomarkers. ELISA method was applied for the determination of serum levels of biomarkers.

**Statistical analysis**

The results were expressed as mean ± SD. One-way ANOVA and  $\chi^2$  tests were performed, using SPSS version 16 (SPSS Inc., Chicago, Illinois, United States). P-values less than 0.05 were considered statistically significant.

**RESULTS**

**Effects of GNPs on macroscopic results of peritoneal adhesions**

All surgical procedures were well tolerated by rats and no infection was observed in animals undergoing surgery. In the control group, severe adhesions were observed between the intestine and peritoneum ( $P < 0.05$ ). In GNP group of 1 ng/ml, one rat had an adhesion, whereas in groups of GNP concentrations of 2.5, 5, 10, 50 and 100 ng/ml, no adhesions were found; in the control group, adhesions were observed in all the rats, as shown in Fig 1 ( $P < 0.05$ ). All GNP groups showed a significant decrease in severity of adhesion, in comparison with the control group. Error! Reference source not found. represents the adhesion formation and division, based on the Adhesion Scoring System (ASS).

**Effects of GNPs on microscopic results of peritoneal adhesions**

Histopathological examinations with respect to inflammation, fibrosis and neovascularization are shown in Fig 2. Microscopic adhesion severity were divided into 4 scores based on inflammation, infiltration and tissue fibrosis; score 1; aggregation of fibrin and neutrophil infiltration that is related to the first step of inflammation, score 2; edema, granulation formation, infiltration and migration of connective tissue that is related to proliferation step, score 3; collagen formation and score 4; fibrous formation. All rats showed a significant decrement in microscopic histopathological examinations, unlike the control group ( $P < 0.05$ ). As it is shown in Fig 2, score 4 of peritoneal adhesion formation was reported in all rats of the control group. Representative Fig of microscopic findings of hematoxylin and eosin H&E) staining, following the intra-peritoneal administration of GNP solutions, is shown in Error! Reference source not found.

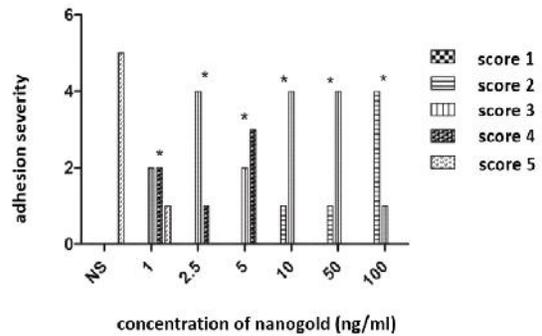


Fig. 1. Comparison of the effects of GNPs on peritoneal macroscopic adhesions in different groups of Wistar rats. Numbers of rats based on adhesion severity scores in GNP (1, 2.5, 5, 10, 50 and 100 ng/ml) and control (NS) groups are shown (\* $P < 0.05$  was considered significant for each group)

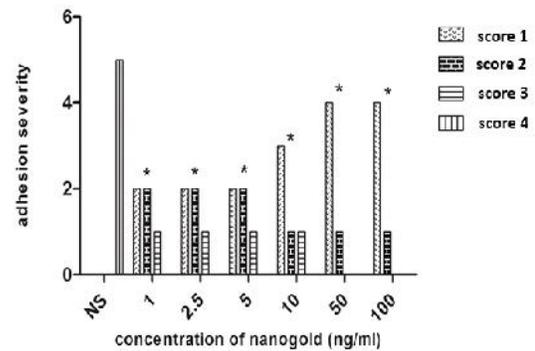


Fig. 2. Comparison of the effects of GNPs on peritoneal microscopic adhesions in different groups of Wistar rats. Numbers of rats based on microscopic findings in GNP (1, 2.5, 5, 10, 50 and 100 ng/ml) and control (NS) groups are shown in the Fig (\*  $P < 0.05$  was considered significant)

**Effects of GNPs on serum concentration of proinflammatory cytokines (TNF, IL-1) and VEGF**

Changes in TNF, IL-1 were compared before and after the intervention. There were no significant differences between the GNP groups and the controls or among the GNP groups 14 days after the surgery (Table 1  $P > 0.05$ ). There were no significant differences among GNP groups and the controls (Table 1. Comparison of changes in TNF, IL-1 serum concentrations in different groups in comparison to control group of Wistar rats.,  $P > 0.05$ ). Furthermore, no significant differences were found among the GNP groups ( $P > 0.05$ ).

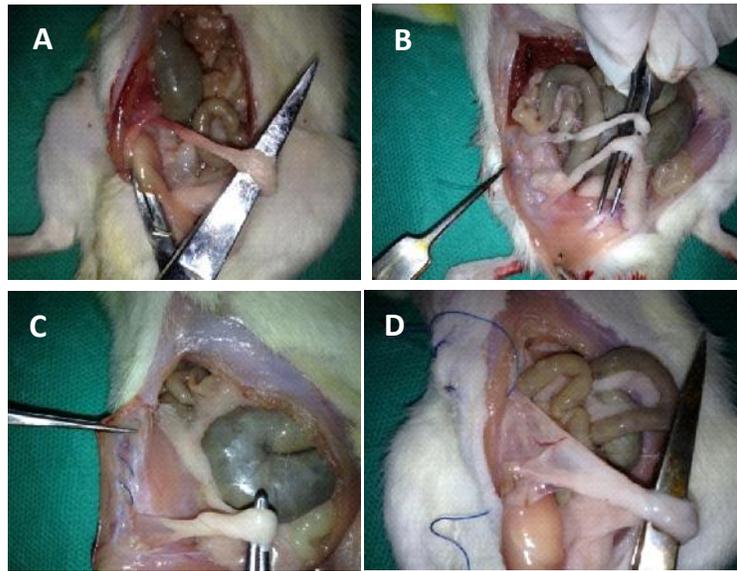


Fig. 3. Adhesion band scores based on ASS method: A: score 1, single, filmy adhesion, B: score 2, more than one filmy adhesion; C: score 3, single, dense adhesion band; D: score 4 single, dense adhesion band with surface adhesion and score 5, more than one dense adhesion band; A and B are related to GNPs and C and D are related to the NS group

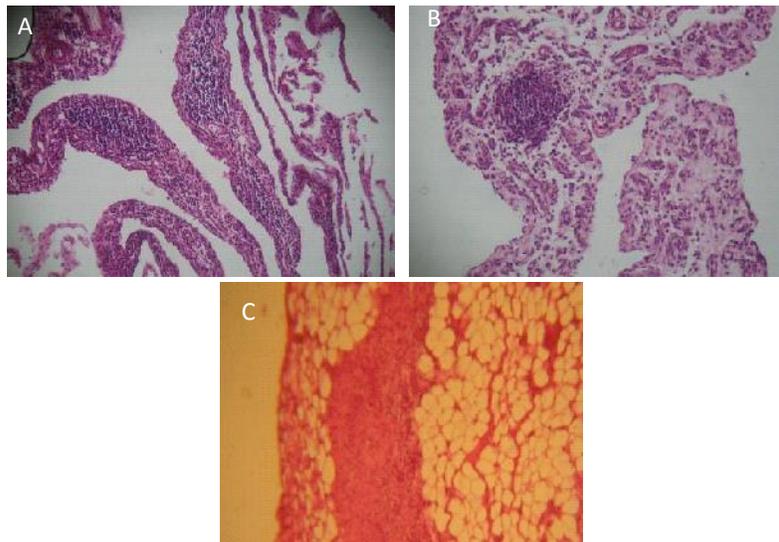


Fig. 4. H&E staining of histological absorption of animal tissues following the administration of GNPs with different concentrations for intraperitoneal lavage. A: fibrillative inflammation and neutrophil infiltration; B: proliferative phase, characterized by the formation of granulation tissues, edema, proliferation, and migration of connective tissue cells; C: scar formation and collagen

## DISCUSSION

Our results showed that intra-abdominal lavage with GNPs (300 nm in diameters) in different concentrations significantly reduced PPA formation at microscopic and macroscopic levels, whereas, it did not reduce the levels of proinflammatory biomarkers including TNF, IL-1 and VEGF. GNPs have been shown to have protective

effects on organs without any toxic effects on animal organs including heart, kidney, liver and brain [23]. The role of inflammation and angiogenesis in peritoneal adhesions has been thoroughly elucidated in previous studies [5, 6, 13, 24, 25]. Following to the injury of peritoneal mesothelium cells, vessels were dilated and

Table 1. Comparison of changes in TNF- $\alpha$ , VEGF and IL-1 serum concentrations in different groups in comparison to control group of Wistar rats

	h TNF- $\alpha$ serum concentration (Pre-Post)*	h VEGF serum concentration (Pre- Post)*	h IL-1 serum concentration (Pre-Post)*
Control group	3.42 $\pm$ 0.17	3.4 $\pm$ 0.02	4.7 $\pm$ 0.02
GNPs (1%)	3.56 $\pm$ 0.32	3.40 $\pm$ 0.09	4.72 $\pm$ 0.02
GNPs (2.5%)	3.47 $\pm$ 0.23	3.49 $\pm$ 0.09	4.74 $\pm$ 0.05
GNPs (5%)	3.44 $\pm$ 0.32	3.50 $\pm$ 0.12	4.76 $\pm$ 0.09
GNPs (10%)	3.61 $\pm$ 0.16	3.39 $\pm$ 0.03	4.77 $\pm$ 0.08
GNPs (50%)	3.33 $\pm$ 0.26	3.39 $\pm$ 0.04	4.69 $\pm$ 0.02
GNPs (100%)	3.62 $\pm$ 0.18	3.41 $\pm$ 0.02	4.70 $\pm$ 0.08

fibrinous exudates infiltrated to the outside of vessels. Fibrous tissue consists of fibroblasts and extracellular matrix that leads to sediment scar formation [26]. After tissue injury, macrophages aggregate in the location and potentiate by inflammatory factors including plasminogen, IL-1, IL-6 and TNF [27] which led to the adhesion of peritoneal site. GNPs showed various anti-inflammatory, anti-oxidant and anti-angiogenic properties and these effects have been mentioned in many different clinical and animal studies [8, 16, 19, 21, 28]. Although the anti-adhesive mechanisms of GNPs are not completely clear, anti-angiogenic and anti-inflammatory effects are likely to be the main reasons for GNPs effects. Some drugs such as COX-2 inhibitors, corticosteroids and immunomodulators, have been used to reduce adhesive bands in animal models and have yielded satisfactory results [11, 29, 30]. Our study is in consistence with a study that was done in animal models and pretreated them with selective and non-selective COX inhibitors to prevent the formation of adhesion bands [30]. The results showed that selective and non-selective COX inhibitors significantly reduced adhesion bands [30]. Another study showed that infliximab (a TNF antagonist) with immunomodulatory effects significantly decreased peritoneal adhesion formation in rats [9]. In a study that was conducted on diabetic mice showed that GNPs have free radical scavenging activities and anti-oxidant effects via activation of glutathione, superoxide dismutase and catalase [23]. In the aforementioned study, it was confirmed that antioxidant and anti-hyperglycemic effects of GNPs are due to inhibiting of reactive oxygen species (ROS) production or balanced ROS generation in streptozocine-induced hyper-glycemic mice; this inhibition showed antioxidant and free radical scavenging effects via increasing levels of antioxidant defense enzymes [23]. Previous studies showed that intra-peritoneal administration of antioxidants posed

anti-adhesive effects [15, 31]. Intra-peritoneal administration of honey and aloe vera gel with antioxidant effects decreased intra-abdominal adhesions [15, 32, 31]. Taken together, the current study showed that GNPs decreased adhesive bands following local administration in peritoneal area but did not reduce serum levels of TNF, IL-1 or VEGF in the GNPs treated group. Explanation for the observed results might include a) given the local administration of GNPs (instead of its systemic application), local content (peritoneal exudates content) level of biomarkers need to be evaluated. If GNPs were administered intravenously, serum levels of mediators such as TNF, IL-1 and VEGF might have significantly changed. Cheong and colleagues showed that peritoneal exudate concentrations of cytokines are different from their serum levels [7]. They showed that adhesion formation within 12h after surgery was correlated with IL-1 and IL-6 intra-peritoneal concentration [7]; b) other adhesive, angiogenic and pro-inflammatory factors in the formation of postoperative adhesion bands may have a role; c) significant changes in the serum levels of biomarkers depends on the pathophysiology of adhesion bands due to the involvement of many factors in their formation; d) if the diameters of GNPs had changed, perhaps, the results would have altered, as well.

**CONCLUSION**

In the present study, it was confirmed that GNPs (300 nm) decreased the formation of postoperative adhesive bands at micro-copic and macroscopic levels. However, no decrement was observed in plasma levels of TNF, IL-1 or VEGF.

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