



Study the efficacy of silver nanoparticles in enhancing tracheal anastomosis healing in rabbits model

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Abstract

This research intended to explore the effect of nano-silver particles on healing anastomosis site in the trachea. Thirty healthy male rabbits were randomly split into control and treated groups equally for this object. Then the rabbits were anesthetized with a mixture of 30 mg/kg B.W (5%) Ketamine and 15 mg/kg B.W of (2%) Xylazine. In the control group, rabbits were induced with tracheal resection and anastomosis. While, rabbits in the treatment group, were induced with the same tracheal resection and anastomosis, a solution containing silver nanoparticles was infiltrated around the anastomosis site, and clinical and histopathological examinations investigated the animals. Clinically all animals had no clinical respiratory illness such as pneumonia, cough, or subcutaneous emphysema, which may occur due to surgical operations. In the control group severe inflammation, which included swelling, pain and redness were seen compared to those of the treated group. The histopathological evaluation of the control group was characterized by granulation tissue and angiogenesis around the suture material with hyperplasia and hypertrophy of goblet cells. Also, there was an intense inflammatory reaction in the mucosa and the presence of normal cartilage with necrosis of the tracheal gland. In the treated group, it was characterized by the development of granulation tissue with angiogenesis and inflammatory cell infiltration with hyperplasia of goblet cells and congestion of blood vessels and normal columnar epithelial cells in mucosa. To summarize, the treatment group's tracheal repair was quicker than to the change in control group.

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Introduction

The trachea is a tube that transports air from the larynx to the lung, eliminating excretions, moistening, warming, and clearing the air from foreign particles through coughing and other interior defensive systems (1). Extended air leak, bronchopleural fistula, and narrowing are the most common trachea surgical consequences (2). Complications can be avoided if the tracheal wound heals adequately. Various treatments have been used to protect from complications, including corticosteroids, vitamin supplements, steroid hormones, granulocyte macrophage, and colony-stimulating factors (3). Tracheal conservation is a difficult thorax surgery, especially when tracheal anastomosis is difficult or

even impossible, or when it fails. Congenital stenosis, trauma and injuries, malignant tumors, tracheoesophageal fistula, poor surgical results for diseases, and tracheal collapse are the most common reasons for tracheal surgery (4). When the length of the resected trachea exceeds 50% in adults or 30% in young ones, initial tracheal resection with straight end-to-end anastomosis following the release of the surrounding anatomical components is insufficient. In order to establish normal airway restoration, tracheal transplant with a substitute is therefore required (5,6). Nanotechnology is the science that deals with materials in the size of 1 to 100 nanometers, and it is significantly unlike the original materials in their properties such as electrical conductance magnetism, chemical reactivity and physical strength (7-9).

Several nanotechnology applications to medicine (nanomedicine) have been used in diagnostics, drug delivery, gene therapy, and general therapeutics (10-12). Drugs for treating of many disorders, such as autoimmune diseases, neuropathy, tumors, and microbial infections, have improved similarly (13-15). Because of their known toxicity against viruses, yeast, and bacteria, metal nanoparticles have been extensively investigated as antibacterial agents (16). The type of metal, structure, size, and high surface area of nanoscale particles, all influence these biological characteristics. Whereas most study now centers on copper and silver, metal oxide nanoparticles like ZnO, TiO₂, CeO₂, MgO, and CaO have also been studied as inorganic antimicrobial drugs (16-18). For several years, silver could be used as an antibacterial and antimicrobial agent (19). Silver particles in the solution are absorbed into microbial cells due to their soluble nature, where they interact with DNA creation and cell division, resulting in an antimicrobial action (20). Silver nanoparticles (Ag NPs) have been found to have low cytotoxic effects and a synergic effect in addition to their antimicrobial qualities, like anti-inflammatory activity, based on their long history and diversified application (19,20). Ag NPs may have additional benefits for treating skin ulcers, fractured bones, wound repair, peripheral nerve damage, and their antibacterial effects (21). Inflammation was reduced after wounds were treated with nano-crystalline silver (22). As a result, the number of interleukins in the wounds decreased, neutrophil apoptosis was influenced, and the level of transforming growth factor was reduced (21-23). Recently, there has been a growing interest in using Ag NPs in various dressings to promote wound healing. A prior analysis exhibited the composite formulation of alginate Ag NPs for wound dressing, exhibiting respectable antibacterial activity. Additionally, Ag NPs can promote wound healing by activating macrophages and regulating fibroblast migration (24).

This study was aimed to explore the effect of nano silver particles on anastomotic tracheal wound healing.

Materials and Methods

Ethical approve

The Experimental Care of Animals and Use Council of the University of Mosul's, College of Veterinary Medicine, approved ethical practices on 7/1/2023. The issue number is UM.VET.2023.039

Experimental design

Thirty, healthy male rabbits (weighing 1.5 to 2 kg and aged between 12-15 months) were used in the current study. Throughout the experiment, all rabbits were kept in individual cages. Animals were randomly assigned to two groups: control and treated (15 animals to each group). Animals in the control group underwent surgery only, while in treated group they underwent surgery with the application

of Ag NPs solution to the anastomosis site. Rabbits were studied by clinical and histopathological examinations.

Silver nanoparticle

Silver nanoparticle powder was purchased from Sigma-Aldrich Chemicals (America), and its color is yellow, form is spherical-shape, and particle size is 20 nm.

Surgical approach

The animals used in the experiment were anesthetized by using an intramuscular mixture of 30 mg/kg B.W (5%) Ketamine and 15 mg/kg B.W of (2%) Xylazine (25-27). From the mandible to the thoracic inlet, the ventral portion of the neck was prepared aseptically, and the cervical trachea was accessed by a ventral midline routing. In the control group, a surgical incision through skin and subcutaneous tissue was created centrally between the manubrium and the larynx. The muscles (sternohyoideus and sternothyroideus) were divided by blunt dissection to observe the trachea. After identifying the resection area, a stay sutures were placed around cartilage rings proximal and distal to the resection area. Two centimeters of the trachea were resected from the identifying area. A tracheal end-to end anastomosis was made using a simple interrupted technique with 5/0 polydioxanone sutures. Muscles and subcutaneous tissues were stitched using a simple continuous pattern using size 2/0 polypropylene suture material, and a simple interrupted approach using silk suture material (size 0) was used to seal the skin incision (28). The treatment group was treated in the same way as the control group, but after completing the anastomosis, a 20 nm Ag NP solution (29) was infiltrated around the anastomotic site. Silver NP solution was prepared by dissolving them in distilled water at a dose of 100 µg / ml (30-32).

Rabbits were checked daily for pulmonary disorders, such as cough, subcutaneous emphysema, or dyspnea. Experimental animals were euthanized and tracheal biopsies were performed after 7, 15, and 30 days post operation for histopathological study. Samples were fixed for at least 72 hours in 10% buffer formalin, and then paraffin blocks were sectioned and dyed with Hematoxylin and Eosin (H&E) for examination.

Results

The present investigation used clinical and histopathological parameters to evaluate the efficiency of silver nanoparticles in tracheal resection and anastomosis healing. Rabbits were observed daily, and all clinical findings were recorded. The body temperature in the treated group was within the standard limit, while the animals in the control group showed a minor rise, exclusively on the first day after surgery. A few observations have been made based on the clinical examination findings; in the control group, inflammatory symbols, which include symptoms of edema

of the surgical site and pain were visualized from the second day after the surgery, then the signs of inflammation gradually disappeared. In the treated group, symptoms and all the signs above were less likely to happen than in the control group. Subcutaneous emphysema was not detected in either experimental group's animals. All animals had no clinical respiratory illness such as pneumonia or cough. The macroscopic examination showed moderate to severe adhesion with surrounding tissues in the control group while there was little or no adhesion with the surrounding tissue in the treated group.

The histopathological evaluation of the control group on the 7th day post-surgery shows that the site of anastomosis is characterized by the presence of granulation tissue and initiation of new blood vessels around the suture material with hyperplasia and hypertrophy of goblet cells in the mucosa. Also, an intense inflammatory reaction was characterized by the infiltration of polymorphonuclear inflammatory cells (Figures 1 and 2).

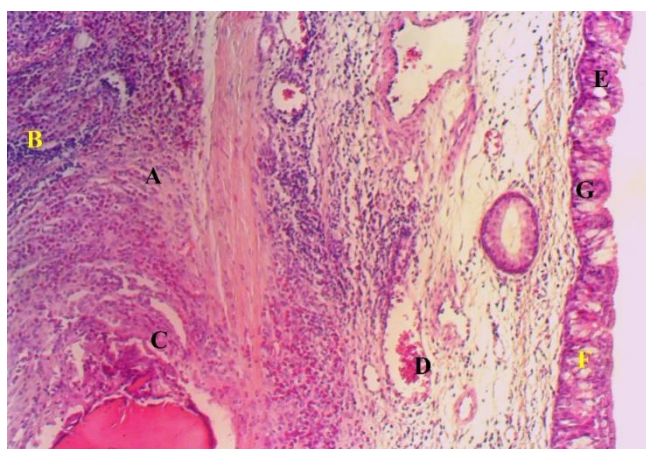


Figure 1: A photomicrograph of the control group on the 7th day post operation shows the site of anastomosis (A), severe inflammatory cell infiltration (B), necrosis (C), congestion (D), hypertrophy (E) hyperplasia of goblet cells (F), and hyperplasia of epithelial cells (G). H&E stain, 100X.

On day 15th post-surgery, there was mononuclear inflammatory cell infiltration with congestion of blood vessels, hyperplasia of epithelial cells, and hypertrophy of goblet cells in mucosa with normal cartilage (Figures 3 and 4). On day 30 post-surgery, a photomicrograph of the trachea showed an inflammatory reaction characterized by inflammatory mononuclear cell infiltration in the submucosa and mucosa with necrosis of the tracheal gland (Figures 5 and 6). While in the treated group, the histopathological results on day 7 post-surgery, the site of the trachea anastomosis were characterized by the development of granulation tissue with new blood vessels (angiogenesis), inflammatory cell infiltration and the presence of suture

material with hyperplasia of goblet cells in the mucosa (Figures 7 and 8). On day 15 post-surgery, a photomicrograph of the trachea shows the inflammatory reaction characterized by inflammatory polymorphonuclear cell infiltration and blood vessels congestion with the development of hyperemia. Also, hyperplasia of epithelial cells was present in the mucosa (Figures 9 and 10). While on day 30 post-surgery, the trachea contained hyperplasia and hypertrophy of goblet cells and normal columnar epithelial cells (Figures 11 and 12).

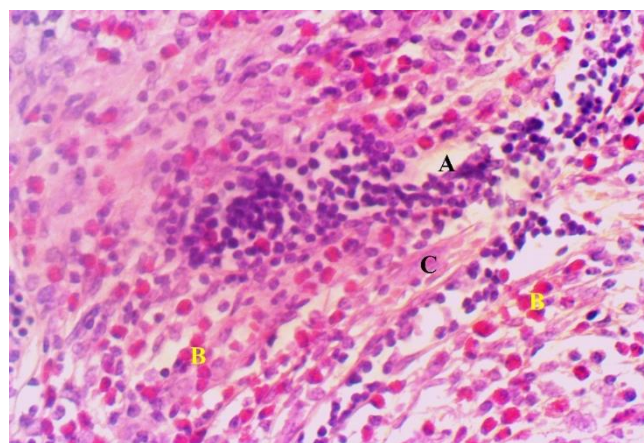


Figure 2: A photomicrograph of the control group on the 7th day post operation shows intense inflammatory reaction characterized by infiltration of polymorphonuclear inflammatory cells (A), hemorrhage (B), and granulation tissue formation (C). H&E stain, 400X.

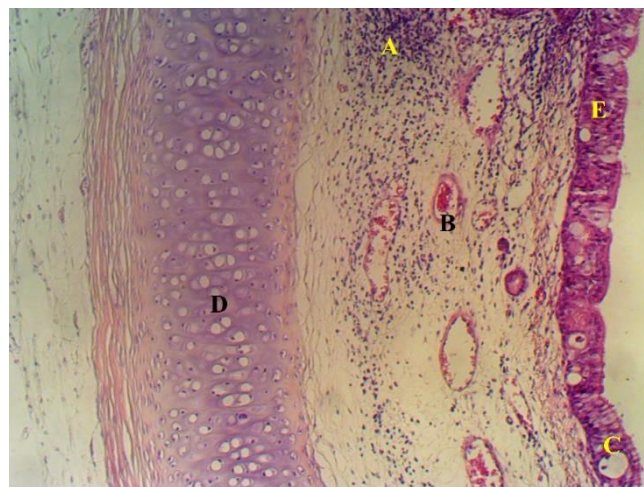


Figure 3: A photomicrograph of the control group on the 15th day post operation shows moderate inflammatory cell infiltration (A), congestion of blood vessels (B), hypertrophy of goblet cells in the mucosa (C) with normal cartilage (D), and hyperplasia of epithelial cells (E). H&E stain, 100X.

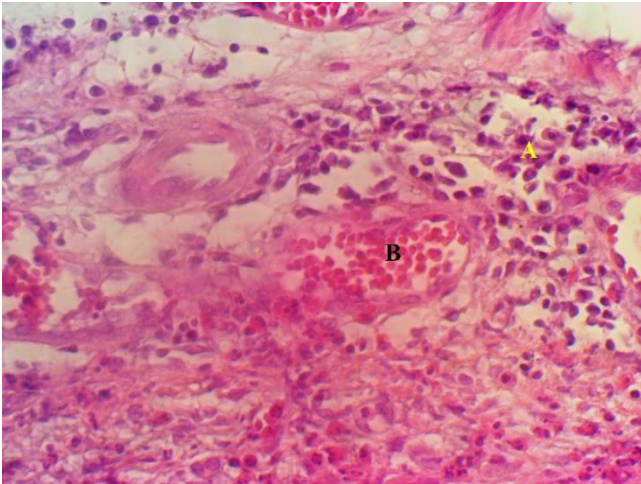


Figure 4: A photomicrograph of the control group on the 15th day post operation shows mononuclear inflammatory cells' invasion during an inflammatory response (A), and blood vessels congestion (B). H&E stain, 100X.

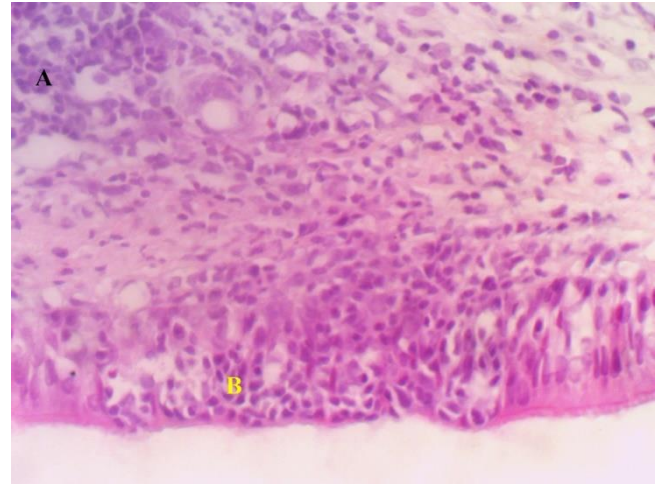


Figure 6: A photomicrograph of the control group on 30th day post operation shows intense infiltration of mononuclear inflammatory cells in the submucosa (A), and mucosa (B). H&E stain, 400X.



Figure 5: A photomicrograph of control group on the 30th day post operation shows intense infiltration of mononuclear inflammatory cells in the submucosa (A), and mucosa (B). H&E stain, 100X.

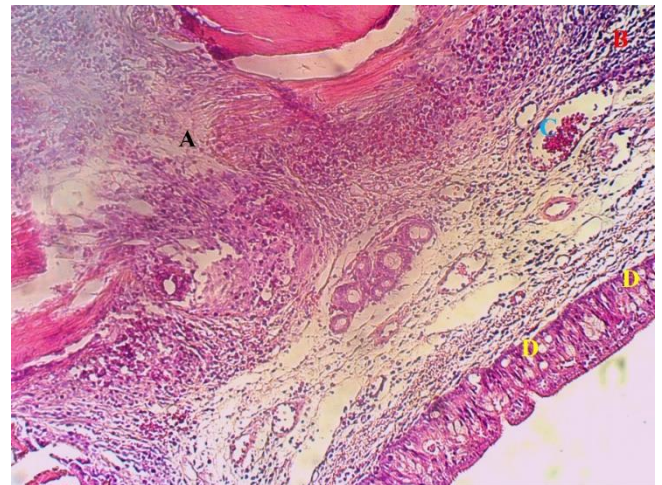


Figure 7: A photomicrograph of the treated group on 7th day post operation shows the site of anastomosis (A), inflammatory cells infiltration (B), congestion (C), hyperplasia of goblet cells (D). H&E stain, 100X.

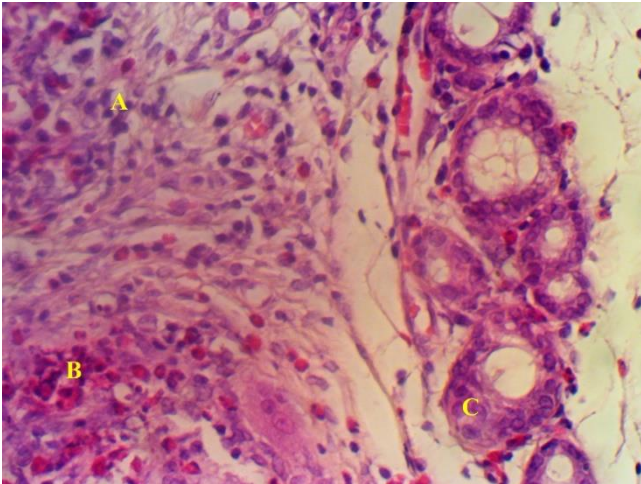


Figure 8: A photomicrograph of the treated group on 7th day post operation shows infiltration of polymorphonuclear inflammatory cells (A), hemorrhage (B), and hyperplasia of epithelial cells of tracheal glands (C). H&E stain, 400X.

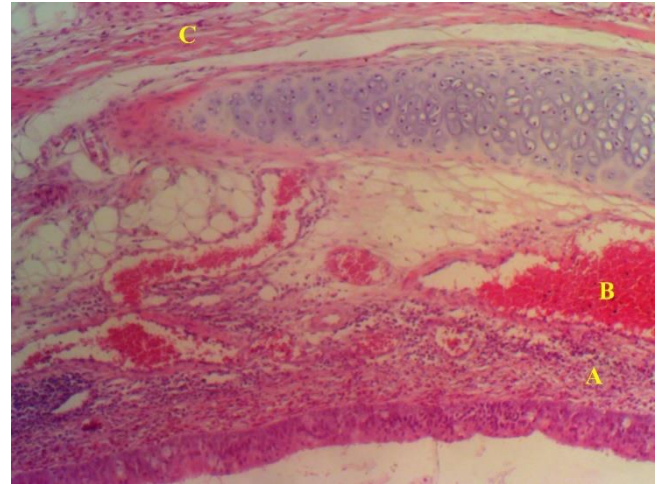


Figure 10: A photomicrograph of the treated group on 15th day post operation shows infiltration of inflammatory cells (A), blood vessels congestion (B), and the presence of collagen fibers and fibroblast (C). H&E stain, 100X.

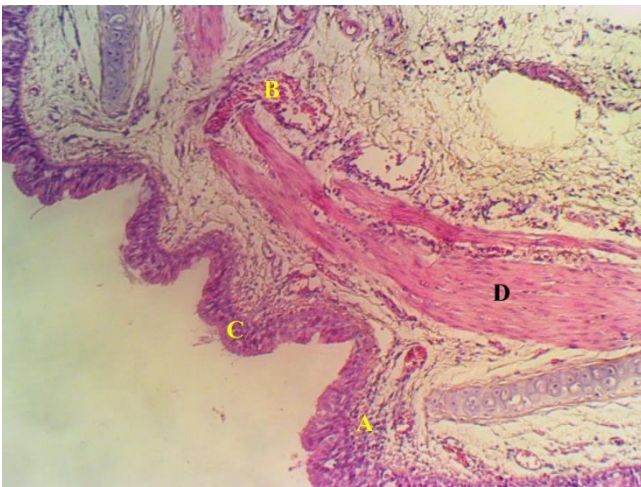


Figure 9: A photomicrograph of the treated group on 15th day post operation shows inflammatory cells infiltration (A), congestion of blood vessels (B), hyperplasia of epithelial cells in the mucosa (C), and myocytes. H&E stain, 100X.

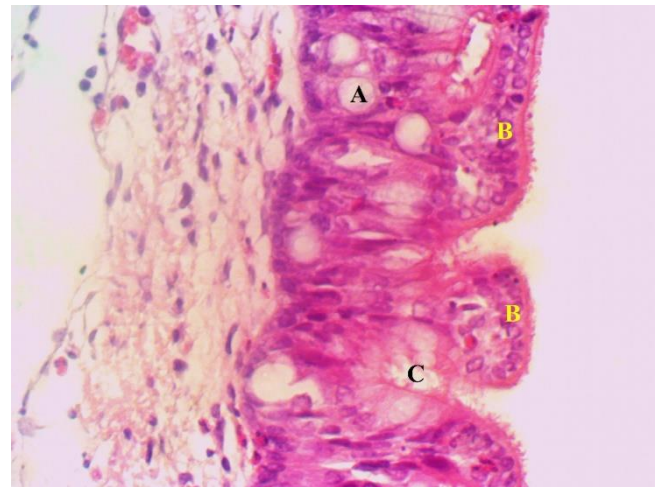


Figure 11: A photomicrograph of treated group on 30th day post operation shows hypertrophy of goblet cells (A), normal columnar epithelial cells (B), and hyperplasia of goblet cells (C). H&E stain, 100X.

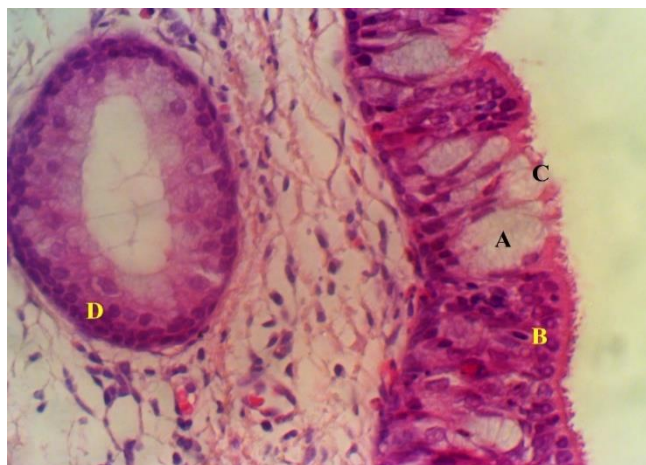


Figure 12: A photomicrograph of the treated group on 30th day post operation shows hypertrophy of goblet cells (A), normal columnar epithelial cells (B), hyperplasia of epithelial cells (C), and hyperplasia of epithelial cells lining tracheal gland (D). H&E stain, 400X.

Discussion

In the control group, body temperature slightly increased in the first days then it returns to its normal level, while the body temperature of the treated group was within usual limits. This difference could be related to nanomaterials' antibacterial and anti-inflammatory properties; Paladini and Pollini (32) and Baygar *et al.* (33) agree with this conclusion, which revealed that silver nanoparticles can accelerate wound healing. Also, Rath *et al.* (34) reported that Ag NPs accelerate wound healing, due to its hemostasis capabilities. Adhesion developed with the surrounding tissues due to inflammatory response to tissue injury in the control group. At the same time, there was little or no adhesion with the surrounding tissue in the treated group.

Wound healing is directly related to the likelihood of a successful surgical treatment. Wounds treated with Ag NPs improved a shortened healing time, and reduced hypertrophic scarring. Furthermore, a higher level of vascular endothelial growth factor was found in keratinocytes along the wound's edge, indicating that Ag NPs may encourage angiogenesis, which promoting wound healing. These findings suggested that Ag NPs could have cosmetic impacts in addition to playing a role in wound healing by controlling different cytokines, particularly inflammatory cytokines (18,35). Ag NPs have the ability to decrease collagen and hydroxyproline levels while increasing keratinocyte migration and proliferation and encourage fibroblast development into myofibroblasts. They could all help with the initial wound adhesion, contraction, and closure. So, Ag NPs provide a beneficial effect in wound repair for both postoperative outcomes and clinical wound management (18,36).

The variation of histopathological findings between both control and treated groups, was due to the presence of silver nanoparticles at the surgical site, which promotes healing by attracting macrophages and fibroblast cells and speeding up apoptosis to eliminate dead cells, also stimulates revascularization and tissue regeneration, all these facts concur with Park *et al.* (37) who demonstrate these results. According to Imani and Safaei (38), using nanoparticles elevates the surface area to volume ratio, which enhances nanoparticle penetrating and interactions with body tissues. Because of the small particle size, it penetrates deeply into tissues and increases cellular absorption. Also, You *et al.* (39) revealed that surface-functionalized nanomaterials modulated the inflammatory process and improved the wound healing proliferation stage through fast fibroblasts and collagen deposition. Kumar *et al.* (40) documented that using Ag NP in wounds led to decreased wound area, fewer macrophages, and more fibroblasts, all were consistent with our findings. Singla *et al.* (41) found that Ag NP can enhance wound healing by increasing collagen and growth factor expression, angiogenesis, promoting re-epithelialization, and collagen deposition. Active involvement of silver nanomaterials in healing process could also be linked to the conversion of fibroblasts into myofibroblasts, which helps to reduce wound size, speed up healing, and increase keratinocyte proliferation and motion resulting in wound reduction and quicker wound closure (42,43). Compared to untreated wounds, silver-treated wounds healed substantially faster. This accelerated wound closure indicates that silver accelerates re-epithelialization, causing keratinocyte growth and metastasis. This was accompanied by a decrease in the production of hypertrophic and keloid granulation tissue, implying that the AG NPs inhibit fibroblast formation or accelerate fibroblast transformation into myofibroblasts (42).

Conclusion

In conclusion, silver nanoparticles can speed up the healing of tracheal wounds while causing a small degree of pathology at the surgical site and decreasing wound healing time, as demonstrated by clinical and histopathological outcomes.

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Conflict of interest

Manuscript author states that neither data nor writing possessed any conflicts of interest.

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دراسة فعالية جزيئات الفضة النانوية في تعزيز شفاء مفاغرة القصبة الهوائية في الأرانب

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الخلاصة

كان الهدف من هذه الدراسة هو دراسة تأثير جزيئات الفضة النانوية على التئام موضع المفاغرة في القصبة الهوائية. تم استخدام ثلاثين أرنبًا ذكراً سليماً قسمت بشكل عشوائي إلى مجموعتين متساويتين سيطرة ومعاملة. تم إجراء التخدير لحيوانات التجربة بإعطاء خليط من الكيتامين (٣٠ ملغم/كغم) والزيلازين (١٥ ملغم/كغم). في مجموعة السيطرة، تم إجراء عملية استئصال القصبة الهوائية والمفاغرة. بينما في مجموعة المعاملة تم تعريض حيوانات التجربة لنفس عملية استئصال القصبة الهوائية والمفاغرة ولكن بعد ذلك تم إضافة محلول يحتوي على جزيئات الفضة النانوية حول موقع المفاغرة، وتم فحص الحيوانات عن طريق الفحوصات السريرية والنسجية. في النتائج السريرية، أظهرت حيوانات مجموعة السيطرة أن لديها تفاعل التهابي شديد بالمقارنة مع مجموعة العلاج، ولم يلاحظ انتفاخ الرئة تحت الجلد في جميع الحيوانات في كلا المجموعتين والذي قد ينتج من العملية الجراحية. لم تكن جميع الحيوانات تعاني من أمراض الجهاز التنفسي السريرية مثل الالتهاب الرئوي أو السعال. أما نتائج التقييم النسيجي المرضي لمجموعة السيطرة تميزت بوجود النسيج الحبيبي وتولد الأوعية الدموية حول مادة الخياطة مع تضخم الخلايا الكأسية. كما كان هناك تفاعل التهابي شديد في الغشاء المخاطي ووجود غضروف طبيعي مع نخر في الغدة الرغامية. بينما في المجموعة المعالجة تميزت بتطور الأنسجة الحبيبية مع تكوين الأوعية الدموية وارتشاح الخلايا الالتهابية مع تضخم الخلايا الكأسية واحتقان الأوعية الدموية والخلايا الظهارية العمودية الطبيعية في الغشاء المخاطي. نستخلص من ذلك أن إصلاح القصبة الهوائية في مجموعة العلاج كان أسرع من مجموعة السيطرة.