REVIEW PAPER

Clinical trials on silver nanoparticles for wound healing

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ABSTRACT

Despite the prevalence of different kinds of wounds among people around the world, challenges ahead for managing wound healing continues. One of the most important issues for wound healing is infection that can delay healing process. Also, drug-resistant infections are growing as a worrying challenge in medicine. A lot of studies done over different methods to improve wound healing process, which in this regard, antibacterial nanoparticles have emerged to market for wound healing. Silver nanoparticles are the first kinds of nanoparticles that emerged in market as a wound dressing for wound healing and some of studies declared their clinical results for silver nanoparticles wound dressing for different kinds of wounds. In this review, we tried to browse clinical trials through using silver nanoparticles for wound healing to peruse the efficacy of silver nanoparticles dressing. The need for more study about efficacy and safety of silver nanoparticles is still a question.

Keywords: *Drug-resistant infection, Silver nanoparticles, Wound*

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INTRODUCTION

During lifetime different events can lead to wound, around one billion people suffer acute or/and chronic wounds. Wound healing is a complex biological process consisting four different phases (hemostasis, inflammation, proliferation, maturation) [1]. The importance of improving healing process of wound is clear and many studies have been done to improve wound healing process. Despite the prevalence of wounds, managing skin damages by medical technology is still inefficient. Many disturbing factor in healing processes can lead to inappropriate healing in dermal and epidermal layers. Confining infection as a disturbing factor is one of challenges for wound healing process [2]. As a challenging and rapidly growing research field, nanotechnology have emerged in wound healing. Many researchers have been tested different nanomaterials for wound healing and some of them like Ag, ZnO, Au, Cu and FeO nanoparticles showed acceptable results on healing process [1].

Silver have been used as an antiseptic agent which can be a broad spectrum antibiotic. It has emerged into ointments and creams since 1968 for topical usages to prevent infection [3, 4]. Blocking the cellular respiration, silver act as an antibacterial agent. Also free silver disrupt bacterial cell membrane function [5]. The important note for Silver nanoparticles is that these kinds of nanoparticles are able to overcome some of the antibiotic-resistant bacteria which can reduce the mortality and the prolonged treatment cost [6]. On the other side, by anti-inflammatory effects and neovascularization, silver nanoparticles can also accelerate the wound healing process [7, 8].

By in vitro and in vivo studies, many researchers has been tested Silver nanoparticle for its antibacterial properties [5]. Silver nanoparticles (AgNPs) is the most commonly used nanoparticles for wound healing, which has emerged in commercially available wound dressing like Acticoat, PolyMem Silver and etc. [2, 9-11]. These kinds of dressing can confine the unwanted release of nanoparticles into the wound area, so

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less probable toxicity might be happen.

Silver nanoparticles have examined for different kinds of ulcers and wounds by researchers, but coming into clinic make it important to investigate its effects on wound in human. Here we mention some clinical trials on wound healing by silver nanoparticles. However, most of the clinical trials over wound healing properties of AgNPs have been used on the burns.

MATERIALS AND METHODS

We tried to review all randomized controlled clinical trials which have been done over silver nanoparticles containing dressing for wound healing. Different sources such as Information Sciences Institute (ISI), PubMed, Google Scholar, Scopus, and Science Direct were used to collect data.

Facing with a big challenge

One of the challenges for pharmaceutical industry is finding an appropriate prevention and treatment for infections causing by bacteria, viruses, fungi, and parasites.

This issue becomes more important in the case of antimicrobial resistance (AMR). AMR related rising mortality because of misusing the existing antibiotics and lack of novel antibiotic agents. Bacterial resistance to conventional antibiotics which is a significant threat to public health make it necessary to find alternative strategies for overcoming this challenge [12]. Using nanoscale materials, as an alternative, is a new promising approach to defeat bacterial resistance. Nanoscale material can interact to the bacteria and act as antibacterial agent via different mechanisms which can be as a solution for bacterial resistance [13, 14].

The antibacterial mechanisms of nanoparticles are different for each kinds of nanoparticles. Nitric oxide-releasing nanoparticles (NO NPs), chitosan-containing nanoparticles (chitosan NPs), silver-containing nanoparticles (Ag NPs), copper-containing nanoparticles, titanium dioxide-containing nanoparticles (TiO2 NPs), zinc oxide-containing nanoparticles (ZnO NPs), and magnesium-containing nanoparticles act as antibacterial agent in different ways. Silver nanoparticles have received considerable attention as antibacterial agent among other metallic nanoparticles and act as antibacterial agent by different mechanisms [13].

Synthesis of silver nanoparticles

Silver nanoparticles find a wide popularity among other nanoparticles for its significant antibacterial properties, however its unique optical, electronic, and antibacterial properties are also valuable. Nanoparticles have been synthesized by two major approaches, including top-down and bottom-up. In top-down methods, bulk materials are used to obtain the nanoscale materials while in bottom-up approach, several atoms, or molecules with molecules, or clusters with clusters were packed [15-17]. Different methods have been reported to synthesis silver nanoparticles, these methods can be divided into chemical, physical, photochemical and biological methods. It is not unexpected that each of these methods has its own advantages and disadvantages, however as an easy method for the synthesis of silver nanoparticles, chemical methods have been used more often. Reduction of silver ions was frequently used to synthesize silver nanoparticles in different studies, the shape and dispersion of nanoparticles can be controlled by different reducing agents. Metal precursors, reducing agents and stabilizing/capping agents are three main components for chemical synthesis of silver nanoparticles [18].

In the case of physical method, a tube furnace at atmospheric pressure can be used to synthesize silver nanoparticles by evaporation-condensation technique [19]. Spark discharging and pyrolysis are conventional physical methods for the synthesis of AgNPs [20, 21].

Due to concerns about toxicity of chemical agents used for the chemical synthesis of silver nanoparticles, many researches for developing safe and reliable approaches are underway. In this regard, instead of chemical reducing agents, biologically derived reducing agents are used. Other items such as microorganismsbes (bacteria and fungi), are also used for the synthesis of silver nanoparticles [22, 23].

Antibacterial mechanism of silver nanoparticles

Ag NPs exert their activity through several antibacterial mechanisms which reduce the possibility of resistance development to Ag NPs. Ag is dissolved in aqueous solution forming Ag^+ ions which act as antimicrobial agent (Fig 1). One of the antibacterial mechanisms of Ag + ions is due to their interaction with sulfur and phosphorus groups in the structure of proteins of the cell wall

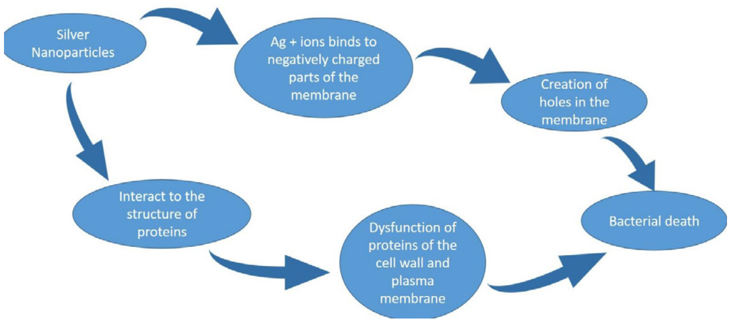

Fig 1. Antibacterial mechanisms of silver nanoparticles

and plasma membrane of bacteria which lead to dysfunction of these proteins thereby threatning organisms life [6]. On the other hand, silver ions bind to negatively charged parts of the membrane thus creating holes in the membrane, causing cytoplasmic contents flowing out of the cell, therefore the proton gradient dissipates across the membrane and finally cause cell death [24]. Thereafter, existence of silver ions inside the cell can disturb the function of electron transport chain of the bacteria. SilverAg + ions also bind to DNA and RNA of the bacteria and inhibit cell division [13].

Wound dressing

Among other applications of silver nanoparticles, its antibacterial property was taken into consideration especially for biomedical applications. Infections, as a big challenge, used up a lot of time and cost for years, also emerging antibiotic resistance as a critical problem makes it indispensable to find an alternative for managing infection.

Silver has been used as an antibacterial agent for years which nowadays, taking the advantages of nanosize materials, silver nanoparticles is emerging as wound dressing. A lot of studies have evaluated the efficacy of silver nanoparticles as an antibacterial agent. After extensive *in vitro* and *in vivo* studies, silver nanoparticles are getting to clinical usage as commercially available products. However, clinical trials are still underway to gather new evidence for possible benefits or side effects of silver nanoparticles. Most studies on silver nanoparticles have been carried out on burns, but other kinds of wounds like diabetic ulcers have also been studied.

One of the commercially available AgNPs containing wound dressing is Acticoat (average size of nanoparticles is 15 nm) which some of case reports for Acticoat on wound healing are available in Smith and Nephew Company's site. Moreover, many studies have been done to find its efficacy and probable adverse effects. Tredge et al., compared Acticoat *versus* silver nitrate solution for burn wounds in 30 patient. Their results showed that the incidence of sepsis was less in Acticoat group, with less pain in comparison with silver nitrate solution [25].

The efficacy of Acticoat for primary burn injuries and other skin injuries in premature neonates evaluated by Rustogi at al. In this study, re-epithelialization happened in all wounds, and positive blood culture and wound infection did not appear during treatment [26]. In another study, Fong at al., determined the effectiveness of Acticoat to treat early burn wounds in comparison with Silvazine (silver sulphadiazine and chlorhexidine digluconate cream). Acticoat reduced the incidence of burn wound cellulitis, and reduced the overall cost of antibiotic usage compared to Silvazine [27]. The effectiveness of silver nanoparticles for healing of second degree burn wound was evaluated in 199 patients in three groups, including silver nanoparticle dressing (group A), 1% silver sulfadiazine cream (group B) and Vaseline gauze (group C). In comparison with group C, reduction in bacterium colonization on wounds was similar for groups A and B, but overall wound healing time was shorter in group A [28].

In another comparative study, the Acticoat versus Silvazine effectiveness was compared for burns dressing in pediatrics, and the results were that the need for grafting was more in Silvazine group versus Acticoat group, and the time taken for re-epithelialization after grafting was less in Acticoat group. However, Acticoat reduced long term scar management versus Silvazine [29]. Acticoat was also tested for exfoliative wounds, and the results indicated that Acticoat had acceptable bacterial protection in the wound area and promoted the wound healing process [30].

Furthermore, nanocrystalline silver was used for lymphatic ulcers by Forner-Cordero and co-workers. Eight patients with lymphatic ulcer were treated with commercially available wound dressings, Acticoat, Algisit and Allevyn. Their protocol employed for healing the lymphatic ulcer was effective to cure ulcers during 1 to 9 weeks and was well accepted by patients [31]. Further study was carried out using crystalline nanosilver wound dressing to evaluate its effect on venous leg ulcers with increased bacterial burden and chronic inflammation. The results showed reduction in wound bacteria and inflammation which promoted healing process of venous leg ulcers [32]. Acticoat was used for post-cardiac surgery mediastinitis in four patients. In spite of applying vacuum-assisted closure (VAC) therapy, physicians were faced with persistently positive microbiological cultures in all four patients. In this study, Acticoat resulted in negative cultures for all four patients within maximum of 72 hours [33].

The efficacy of nanocrystalline silver and cadexomer iodine was compared in preventing infection in leg ulcers. Immediate reduction in wound size was obtained by the nanocrystalline silver in comparison with cadexomer iodine [34]. Nanocrystalline silver wound dressing and hydro surgical debridement were compared and used for Gustilo/Anderson type II and III fractures. Positive culture and clinical infection were confirmed prior to using nanocrystalline silver wound dressing and hydro-surgical debridement. In this study, nanocrystalin silver was able to confine infection and improved wound healing [35].

In another study, Acticoat was compared with plain gauze for initial post debridement management of military wounds. Wound healing process was examined in 76 patients via microbiological assessment. This study did not reveal differences in wound healing and colonization between 2 groups, while unpleasant odor was reduced in patients receiving Acticoat [36].

Nanocrystalline silver dressing (Acticoat^R) was compared with regular silver sulfadiazine dressing (control) by Masjedi et al. Qualitative wound score was more in Acticoat^R group, and the healing time was shorter in comparison to control group [37]. Topical silver nanogel versus conventional dressing was also tested by Sharma et al. The results showed good antibacterial and anti-inflammatory effects in wound area [38].

When nanosilver dressing and povidone iodine dressing were copared in patients with chronic diabetic foot ulcers, it was shown that nanosilver promoted the healing process and hospital stay was shorter in nanosilver group [39]. Silver nanoparticels for anorectal surgery was evaluated by Wang et al., and their results indicated that the rate of epithelialization was significantly faster compared to control group. Moreover, wound healing process was improved by using silver nanoparticles [40].

As it is not unexpected, each dressing might have its imperfection, comparing Acticoat dressing with Aquacel Ag dressing indicated similar healing development and bacterial control, but Aquacel Ag dressing was more costly, effective and comfortable for patients [41].

Toxicity is probably another issue which 0can be concern for using either Acticoat dressing or silver nanoparticles containing dressing. Trop et al., reported that using Acticoat dressing for burn patients led to raised liver enzymes along emersion of argyria like symptoms [42].

Another important concern about silver nanoparticles is for its possible unwanted or toxic effects to environment. Threat of silver nanoparticles to soil, water and other living creatures is of major concern. Furthermore, bacterial resistance to silver nanoparticles among beneficial microorganism might be a crucial concern [43].

DISCUSSION

The process of wound healing can be affected by different factors which can promote or postpone the healing process. One of the most important factors is infection in wound area that can prolong healing time which can also increase morbidity or mortality via resistance to antibiotic. Prevention of infection in wound area can be crucial for wound healing, and thus various kinds of strategies have been used for preventing wound area infections [1, 5]. Because of antibiotic resistance, other kinds of antibacterial agents have emerged such as antibacterial nanoparticles.

Silver nanoparticles were evaluated in different studies for its antibacterial properties that can affect the healing process. It proved by different studies that silver nanoparticles can eliminate infection thereby promoting the wound healing process. In addition, different studies proved that silver nanoparticles can improve re-epithelialization in wound area. Most studies on wound healing properties of silver nanoparticle revealed the efficacy of silver nanoparticle containing dressing to improve healing of different kinds of wounds, but a significant shortage of clinical trials is felt for evaluating the posssible toxicity and side effects of silver nanoparticles dressing.

CONCLUSION

Most studies reported that silver nanoparticles dressing has the potential to be used as an effective antibacterial agent for wound healing. However, clinical trials on the possible toxicity via dermal exposure are not sufficient enough, and thus more clinical studies are recommended on the potential toxicity via dermal exposure of silver nanoparticles.

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REFERENCES

1. Rex Jeya Rajkumar S, MSA Muthukumar Nadar, Paulraj Mosae Selvakumar. Nanotechnology in Wound Healing-A Review. Glob J Nano. 2017; 3(1): 1-4.
2. Nam G, Rangasamy S, Purushothaman B, Song JM. The application of bactericidal silver nanoparticles in wound treatment. Nanomater Nanotechnol. 2015; 5-23.
3. Fox CL. Silver sulfadiazine—a new topical therapy for pseudomonas in burns: therapy of pseudomonas infection in burns. Arch Surg. 1968; 96(2): 184-188.
4. Hoffmann S. Silver sulfadiazine: an antibacterial agent for topical use in burns. Scand J Plast Reconstr Surg. 1984; 18(1): 119-126.
5. Fong J, Wood F. Nanocrystalline silver dressings in wound management: a review. Int J Nanomedicine. 2006; 1(4): 441-449.
6. Lara HH, Ayala-Núnez NV, Turrent LdCI, Padilla CR. Bactericidal effect of silver nanoparticles against multidrug-resistant bacteria. World J Microbiol Biotechnol. 2010; 26(4): 615-621.
7. Nadworny PL, Wang J, Tredget EE, Burrell RE. Anti-inflammatory activity of nanocrystalline silver in a porcine contact dermatitis model. Nanomedicine. 2008; 4(3): 241-251.
8. Lansdown AB. A pharmacological and toxicological profile of silver as an antimicrobial agent in medical devices. Adv Pharmacol Sci. 2010; 2010: 910686.
9. Pannerselvam B, Jothinathan MKD, Rajenderan M, Perumal P, Thangavelu KP, Kim HJ, Rangarajulu, SK. An in vitro study on the burn wound healing activity of cotton fabrics incorporated with phytosynthesized silver nanoparticles in male Wistar albino rats. Eur J Pharm Sci. 2017; 100: 187-196.
10. Boonkaew B, Kempf M, Kimble R, Supaphol P, Cuttle L. Antimicrobial efficacy of a novel silver hydrogel dressing compared to two common silver burn wound dressings: Acticoat™ and PolyMem Silver®. Burns. 2014; 40(1): 89-96.
11. Dunn K, Edwards-Jones V. The role of Acticoat™ with nanocrystalline silver in the management of burns. Burns. 2004; 30: S1-S9.
12. Blair JM, Webber MA, Baylay AJ, Ogbolu DO, Piddock LJ. Molecular mechanisms of antibiotic resistance. Nat Rev Microbiol. 2015; 13(1): 42-51.
13. Pelgrift RY, Friedman AJ. Nanotechnology as a therapeutic tool to combat microbial resistance. Adv Drug Deliv Rev. 2013; 65(13): 1803-1815.
14. Zewde B, Ambaye A, III JS, Raghavan D. A Review of Stabilized Silver Nanoparticles–Synthesis, Biological Properties, Characterization, and Potential Areas of Applications. JSM Nanotechnol Nanomed. 2016; 4(2): 1043.
15. Wei L, Lu J, Xu H, Patel A, Chen Z-S, Chen G. Silver nanoparticles: synthesis, properties, and therapeutic applications. Drug Discov Today. 2015; 20(5): 595-601.
16. Zhang X-F, Liu Z-G, Shen W, Gurunathan S. Silver nanoparticles: synthesis, characterization, properties, applications, and therapeutic approaches. Int J Mol Sci. 2016; 17(9): 1534.
17. Deepak V, Umamaheshwaran PS, Guhan K, Nanthini RA, Krithiga B, Jaithoon NMH, Gurunathan S. Synthesis of gold and silver nanoparticles using purified URAK. Colloids Surf B Biointerfaces. 2011; 86(2): 353-358.
18. Tran QH, Le A-T. Silver nanoparticles: synthesis, properties, toxicology, applications and perspectives. Adv Nat Sci Nanosci Nanotechnol. 2013; 4(3): 1-20.
19. Iravani S, Korbekandi H, Mirmohammadi SV, Zolfaghari B. Synthesis of silver nanoparticles: chemical, physical and biological methods. Res Pharm Sci. 2014; 9(6): 385-406.
20. Tien D, Liao C, Huang J, Tseng K, Lung J, Tsung T, WS Kao, TH Tsai, TW Cheng, BS Yu, HM Lin, L Stobinski. Novel technique for preparing a nano-silver water suspension by the arc-discharge method. Rev Adv Mater Sci. 2008; 18: 750-756.
21. Pluym T, Powell Q, Gurav A, Ward T, Kodas T, Wang L, Glicksman HD. Solid silver particle production by spray pyrolysis. J Aerosol Sci. 1993; 24(3): 383-392.
22. Khan M, Tarek F, Nuzat M, Momin M, Hasan M. Rapid Biological Synthesis of Silver Nanoparticles from Ocimum sanctum and Their Characterization. J Nanosci. 2017; 1-7
23. Gudikandula K, Charya Maringanti S. Synthesis of silver nanoparticles by chemical and biological methods and their antimicrobial properties. J Exp Nanosci. 2016; 11(9): 714-721.
24. Knetsch ML, Koole LH. New strategies in the development of antimicrobial coatings: the example of increasing usage of silver and silver nanoparticles. Polymers. 2011; 3(1): 340-366.
25. Tredget EE, Shankowsky HA, Groeneveld A, Burrell R. A Matched-Pair, Randomized Study Evaluating the Efficacy and Safety of Acticoat* Silver-Coated Dressing for the Treatment of Burn Wounds. J Burn Care Res. 1998; 19(6): 531-537.
26. Rustogi R, Mill J, Fraser J, Kimble R. The use of Acticoat™ in neonatal burns. Burns. 2005; 31(7): 878-882.
27. Fong J, Wood F, Fowler B. A silver coated dressing reduces the incidence of early burn wound cellulitis and associated costs of inpatient treatment: comparative patient care

audits. Burns. 2005; 31(5): 562-567.

28. Chen J, Han C, Lin X, Tang Z, Su S. Effect of silver nanoparticle dressing on second degree burn wound. Zhonghua wai ke za zhi [Chinese journal of surgery]. 2006; 44(1): 50-52.
29. Cuttle L, Naidu S, Mill J, Hoskins W, Das K, Kimble RM. A retrospective cohort study of Acticoat versus Silvazine in a paediatric population. Burns. 2007; 33(6): 701-707.
30. Yang JY, Huang CY, Chuang SS, Chen CC. A clinical experience of treating exfoliative wounds using nanocrystalline silver-containing dressings (Acticoat®). Burns. 2007; 33(6): 793-797.
31. Forner Cordero I, Navarro Monsoliu R, Munoz Langa J, Alcober Fuster P, Rel Monzo P. Use of a nanocrystalline silver dressing on lymphatic ulcers in patients with chronic lymphoedema. JWC. 2007; 16(5): 235-239.
32. Sibbald RG, Contreras Ruiz J, Coutts P, Fierheller M, Rothman A, Woo K. Bacteriology, inflammation, and healing: a study of nanocrystalline silver dressings in chronic venous leg ulcers. Adv Skin Wound Care. 2007; 20(10): 549-558.
33. Totaro P, Rambaldini M. Efficacy of antimicrobial activity of slow release silver nanoparticles dressing in post-cardiac surgery mediastinitis. ICVTS. 2009; 8(1): 153-154.
34. Miller CN, Newall N, Kapp SE, Lewin G, Karimi L, Carville K, Gliddon T, Nick M, Santamaria RN. A randomized-controlled trial comparing cadexomer iodine and nanocrystalline silver on the healing of leg ulcers. Wound Repair Regen. 2010; 18(4): 359-367.
35. Keen JS, Desai PP, Smith CS, Suk M. Efficacy of hydrosurgical debridement and nanocrystalline silver dressings for infection prevention in type II and III open injuries. IWJ. 2012; 9(1): 7-13.
36. Fries C, Ayalew Y, Penn-Barwell J, Porter K, Jeffery S, Midwinter M. Prospective randomised controlled trial of nanocrystalline silver dressing versus plain gauze as the initial post-debridement management of military wounds on wound microbiology and healing. Injury. 2014; 45(7): 1111-1116.
37. Masjedi H, Malekzad F, Marashian SM, Younespour S. The healing effect of nano-silver dressings in pemphigus vulgaris. Wounds. 2015; 2(2).
38. Sharma R, Kumar R, Mittal S, Kaur A. Study of effect of topical nano silver gel on wound healing. J Adv Med Dent Scie Res. 2016; 4(5): 59.
39. Rahaman A, Manjunath A, Bhattacharya AM. Nanosilver versus Povidone iodine dressing-efficacy in the management of chronic diabetic foot ulcers. JEMDS. 2017; 6(22): 1799-1803.
40. Wang Y, Qiao Y, Wang P, Li Q, Xia C, Ju M. Bio fabrication of silver nanoparticles as an effective wound healing agent in the wound care after anorectal surgery. J Photochem Photobiol B. 2018; 178: 457-462.