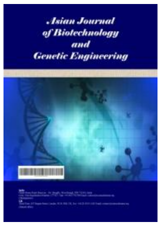

Asian Journal of Biotechnology and Genetic Engineering

3(2): 37-45, 2020; Article no.AJBGE.59312

Recent Advances and Perspectives of Silver Nanotechnology in Surgery and Dentistry

Andrei Zbuchea[1*], Carmen Chelmuş[2,3], Elina Teodorescu[4] and Ştefan Milicescu[4]

[1]Plastic Surgery Department, District Emergency Hospital, 100th Găgeni Street, Ploieşti, Romania.
[2]Plastic Surgery Department, District Emergency Hospital, 177th Brăilei Street, Galati, Romania.
[3]Faculty of Medicine, Dunărea de Jos University, 47th Domnească Street, Galaţi, Romania.
[4]Faculty of Dental Medicine, Carol Davila University of Medicine and Pharmacy, 17-23rd Calea Plevnei, Bucharest, Romania.

Authors' contributions

This work was carried out in collaboration among all authors. Author AZ designed the study, performed the analysis and wrote the first draft of the manuscript. Authors CC and ET managed the analyses of the study. Author SM managed the literature searches. All authors read and approved the final manuscript.

Article Information

Editor(s):
(1) Dr. S. Prabhu, Sri Venkateswara College of Engineering, India.
Reviewers:
(1) Álvaro de Jesús Ruíz Baltazar, Universidad Nacional Autónoma de México, México.
(2) Prof. Dr. Hajir Ali Shareef, Kirkuk University, Iraq.
(3) Dr. Kavita Verma, Sankalchand Patel University, India.
Complete Peer review History: http://www.sdiarticle4.com/review-history/59312

Mini-review Article

Received 29 May 2020
Accepted 05 August 2020
Published 12 August 2020

ABSTRACT

Over time, different silver preparations have maintained a sustained interest from the medical community. The article highlights the up-to-date knowledge on qualities, properties and applications of the colloidal silver in the field of surgery and dentistry. It aims to provide a synthesis of current issues regarding the complex action of colloidal silver on burn wounds and analyzes the anti-infectious, anti-inflammatory and wound healing properties of modern silver releasing systems. The silver nanoparticles have also been implemented in various fields of dentistry, including dental prostheses, implantology, restorative and endodontic dentistry, with very promising results.

**Corresponding author: E-mail: a_zbuchea@yahoo.com;*

Keywords: Silver dressings; nanocrystalline silver; burns; wound healing.

1. INTRODUCTION

Especially due to its intrinsic and non-toxic anti-infectious activity, the silver has been used in medicine since ancient times and in different formulations. Silver was the most important antimicrobial agent available before the introduction of antibiotics. In the 1880 s, Carl Credé, a German obstetrician, introduced the use of silver nitrate eye drops as an antiseptic for the prevention of ophthalmia neonatorum in newborns [1,2]. The surgeon B. Credé, Carl Credé's son, is accredited as the first to use colloidal silver for wound antisepsis in 1891, after observing Halsted applying silver foil to infected wounds [1,3].

The electric colloids of silver became the standard of antimicrobial therapy in the first part of the 20th Century until the emergence of antibiotics in the early 1940 s, together with the complexes of silver and protein known as mild silver proteins [1]. In present, the silver ion is the most commonly used antimicrobial agent in the topical treatment of burns and silver sulfadiazine (SSD), introduced by Fox in 1968, is the gold standard for the burns treatment.

2. MATERIALS AND METHODS

A huge amount of observations and results is available in the literature regarding the use of various silver formulations in surgery and dentistry. These data are available from databases, such as Medline, from journals, such as Burns, from search engines and from specialized books. This article has performed comprehensive analyses of silver nano-particles, by selecting the most reliable and representative studies, without applying any restrictions regarding the source or date of publication.

The complex activity of silver nano-particles in burns and other types of wounds has been evidenced by its anti-infectious and wound healing properties, as revealed from the studies undertaken. The effectiveness of topical administration of silver nano-particles preparations has been highlighted both by a series of laboratory experiments, and also by clinical trials. Advantages, application procedures and risks of silver administration have been also investigated, together with a significant series of recent uses of silver nano-particles in various fields of dentistry, including dental prostheses, implantology, restorative and endodontic dentistry.

3. RESULTS AND DISCUSSION

3.1 The Anti-infectious Activity of Silver

Much more potent than any antibiotic, silver has been proved a very broad-spectrum anti-microbial agent, against some 650 micro-organisms, yeast, mold and bacteria [4], including methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE) and multidrug-resistant (MDR) Pseudomonas aeruginosa [5-8]. Moreover, studies revealed that the prevalence of bacterial resistance was low [9] and that the anti-infectious effect of the silver dressings increased when pH became more acidic [7].

Silver nano-particles (AgNPs) also exert antimicrobial properties against bacteria and viruses [10,11] with close attachment of the nano-particles to the bacterial cells or to the virus particles. The bactericidal properties of the nano-particles are size dependent, as the nano-particles that interact directly with the bacteria preferentially have a diameter ranging from 1 to 10 nm [12]. However, the main anti-infectious activity of silver results from the production of silver ions within an aqueous environment.

Silver ions manifest a complex approach of anti-infectious activity. Antimicrobial action depends on the intracellular accumulation of low concentrations of silver ions. These avidly bind to negatively charged components in proteins and nucleic acids, thereby inducing structural changes in bacterial cell walls, membranes and nucleic acids that affect viability. Silver ions alter microbial functions through multiple harmful effects rather than specific disturbances, through simultaneous interaction with amines, thiol, phosphates, carboxylates, hydroxyls, indoles and imidazoles groups [13]. Thus, they interact with a wide range of molecular processes within microorganisms and produce a range of effects from inhibition of growth, loss of infectivity, to cell death. The anti-infectious capacity depends on both the concentration of silver ions and the sensitivity of the microbes. The spectrum of activity is very wide and the occurrence of bacterial resistance is relatively low, especially in clinical cases [14].

In modern times of bacterial multi-resistance to antibiotics, the broad-spectrum anti-infectious activity and the significantly low bacterial resistance have made silver a very important agent in the wound care armamentarium [15]. In contrast to conventional antibiotics, an aspect of particular interest is the significant anti-biofilms activity of silver against different microorganisms, including staphylococci and Pseudomonas aeruginosa [16-19].

3.2 The Influence on Wound Healing

Due to the anti-infectious activity and to the decrease of the bacterial burden, silver has an essential contribution to the proper wound healing, as the increased bacterial load can delay wound healing by multiple mechanisms [6,20]. In addition to the anti-infectious effect, silver has proven a significant anti-inflammatory activity [21], which has been evidenced by the decrease in erythema and edema and by the increased wound healing. The anti-inflammatory action depends on the delivery vehicle, on the duration of release and on the available concentration and species of silver [5]. Quantitative PCR, proteomic and immunohistochemical studies highlighted the fast and effective wound healing activity of silver nanoparticles, as a result of their antimicrobial actions, decrease of wound inflammation and modulation of fibrogenic cytokines, in a dose dependent way [20].

The anti-inflammatory activity in the nanocrystalline silver-treated wounds has been associated with:

- The increased inflammatory cell apoptosis.
- The decreased expression of proinflammatory cytokines (TNF-α).
- The decreased gelatinase activity [21-23].

Ag°, which is found in nanocrystalline silver and in colloidal silver and which is probably released in a cluster form, is the most likely species to have anti-inflammatory activity, as other noble metals have demonstrated similar activity [23]. The application of silver nitrate induced apoptosis in all cell types, including keratinocytes, resulting in delayed wound healing [22].

A special biochemical aspect in wound healing is the relationship between tissue destruction by a group of collagenase enzymes known as matrix metalloproteinases (MMP) and tissue synthesis which is stimulated by growth factors. The matrix metalloproteinases facilitate wound healing, but excessive levels degrade fibronectin and peptide growth factors. The silver preparations provide additional benefits by down-regulating MMPs to levels that alter the inflammatory events and contribute to faster wound healing. The nanocrystalline silver dressings modulate the inflammatory process at or above the level of TNF-α expression, thus generating an anti-inflammatory effect [5].

3.3 Silver Releasing Systems - Nanocrystalline Silver Dressings

The nanocrystalline silver dressings were developed and introduced in the late 1990 s and represent the latest forms of silver wound dressings. These products have been created to exceed some of the drawbacks of the previous silver dressings [24], as they represent further improvement in prolongation of silver delivery, with sustained release of silver in a less rapidly deactivated form [25]. The nanocrystalline silver technology is able to more consistently maintain adequate antibacterial concentrations with good residual activity, keeping elevated levels over longer periods of time [24]. These wound dressings generally appear to stimulate healing, as well as inhibiting micro-organisms.

The nanocrystalline silver is deactivated much more slowly and provides a broad initial bolus followed by a continuous release of silver into the wound, as uncharged nanocrystalline silver reacts less with the negatively charged particles in the wound bed [24].

Besides the more substantial effective dose of silver, an additional benefit of nanocrystalline formulations is less frequent dressing changes, on the order of days as compared to standard, once-to twice daily dressing changes for SSD and up to twelve times per day for silver nitrate. This frequency improves patient comfort as well as provides wound healing due to favorable moist environment and to less disruption to the newly formed epithelium [24].

As with other wound topical applications, the evaluation of silver impregnated dressings has been accomplished by in vitro antibacterial studies, animal models and clinical trials. A large number of studies have assessed different silver releasing dressings [26-35] and have revealed that, compared to SSD, they have increased wounds healing, decreased pain symptoms and increased patient convenience because of limiting the frequency of dressing changes, even at lower total cost. Moreover, serum silver levels in the case of some silver releasing dressings (eg Acticoat) were elevated, but remained similar to that reported following the use of silver sulfadiazine [36]. However, various silver concentrations and different modes of silver ions delivery make the direct comparison inappropriate [13].

Moreover, silver-based technologies can provide added benefits, such as down-regulation of MMPs to levels that facilitate wound healing. Silver is a powerful, broad-spectrum antimicrobial with anti-inflammatory and healing properties, but only if it is delivered at the right concentration and species and over an appropriate interval of time. In particular, the nanocrystalline silver dressings meet these requirements. When the heavy bacterial burden in a wound is eradicated, the wound is turned back to an appropriate healing pathway [20]. Also, the inflamed wounds can benefit from the application of silver dressings, due to the anti-inflammatory effect highlighted in experimental studies [27,37].

As a general classification, the silver component of dressings may appear:

- As a coating, on one or both outer surfaces of the dressing.
- Within the structure of the dressing, either as a coating on dressing materials, within the spaces of the dressing materials, or as a compound that forms part of the dressing structure (eg silver alginate).
- As a combination of these [38].

Silver on the surface of the dressing comes into direct contact with the wound bed where it exerts the antimicrobial action. Silver within the dressing structure acts on bacteria absorbed into the dressing with wound exudate, but may also diffuse to some extent into the wound [26,38].

The total amount of silver delivered to wounds varies considerably between different dressings [26]. Into the wound environment, the amount of available silver decreases further due to the interaction of the ionized silver (in the aqueous environment) with exudate and wound components such as chloride ions and proteins, which chelate free silver ion or precipitate it as an insoluble salt (eg silver chloride), inhibiting antibacterial action [5,38]. Whilst in some laboratory experiments very low concentrations of silver nanoparticles (1ppm or less) have been evidenced to be effective against bacteria [39], it is unclear how quantity and availability of silver measured experimentally can relate to clinical effectiveness [26,38].

The main concern about the application of antiseptics and antimicrobial agents on open wounds is their potential for cytotoxicity to cells implicated in wound healing process, such as keratinocytes and fibroblasts, primarily *In vitro* encountered and concentration dependent [26,40]. Even since 1919, Fleming has stated that anything that is bactericidal may well be tissuecidal [41]. Some silver-containing antimicrobials agents have been found to exert cytotoxic effects on wound tissue and to inhibit keratinocyte proliferation [42-44]. Also, using them on open wounds may be injurious to fibroblasts and may inhibit wound healing [40,45,46].

Nevertheless, despite some in vitro cytotoxicity, in general the silver-releasing dressings appeared to promote healing of the wounds [47-49]. Just as in vitro bacteriologic evaluation of an antimicrobial do not fully predict its effect in the *In vivo* or clinical circumstances, *In vitro* cytotoxicity tests do not fully predict the effect of an agent on wound healing intricate processes. Due to the different antimicrobial and wound healing properties among manufactured products, a careful consideration of the particular effects is needed when deciding on use of a specific silver-containing dressing. Studies revealed that healing was accelerated with the use of most of the silver-containing dressings. The effective decrease of the tissue bacterial load seemed to be the best predictor of acceleration of healing. Thus, studies revealed that Actisorb, Acticoat Absorbent, and Urgotul SSD had the most rapid wound healing and also effective in vivo antimicrobial activities, when different types of silver dressings were evaluated: Acticoat 7 (Smith and Nephew, London, UK), Acticoat Absorbent (Smith and Nephew, London, UK), Acticoat Moisture Control (Smith and Nephew, London, UK), Actisorb (Systagenix, North Yorkshire, UK), Aquacel Ag (ConvaTecInc, Skillman, New Jersey), Contreet Foam (Coloplast, Minneapolis, Minnesota), Silvercel (Systagenix, North Yorkshire, UK), Urgotul SSD (silver sulfadiazine) (LaboratoireUrgo, Chenove, France) and Silverlon (Cura Surgical, Geneva, Illinois) [41].

Silver formulations have been assessed in a series of controlled clinical studies, many of which have compared SSD with silver-containing dressings. RCTs have been performed in a range of acute and chronic wounds, searching different endpoints [38]:

- Bacteriological endpoints (improvement of bacteriological status) [50,51].
- Clinical indicators of infection (signs of heavy bacterial colonization) [52,53].
- Endpoints related to healing (level of pain, healing rate, time to complete wound healing, frequency of dressings changes) [54-57].

RCTs, systematic reviews and meta-analyses of silver dressings for superficial and partial thickness burns and for split skin donor sites have evidenced that SSD was consistently associated with poorer healing outcomes than silver-containing dressings, biosynthetic (skin substitute) dressings and silicon-coated dressings. Silver-impregnated dressings heal burns more quickly than SSD, although the evidence is of poor quality [58].

All these studies have indicated that silver dressings are associated with factors that may be beneficial in terms of cost effectiveness [38]:

- Decreased time to wound healing [29].
- Shorter hospitalization time [59,60].
- Reduced frequency of dressing changes [55,56].
- Reduced need for pain medication during dressing change [55].

Several silver dressing studies have revealed beneficial effects on overall charges of wound management and on quality of life parameters [55,56,59,60]. The nanocrystalline silver dressings are generally no more expensive than other types of antimicrobial dressings [38].

3.4 Nanocrystalline Silver in Dentistry

AgNPs have also been used in several areas of dentistry, as endodontics [61], dental prostheses [62], implantology [63], and restorative dentistry [64], in order to avoid or at least to decrease the microbial colonization and biofilm accumulation over dental materials, to ameliorate oral health and to improve life quality [65,66]. AgNPs could also decrease the significant clinical and economic impact of caries, by stimulating the remineralization process and controlling biofilm development [15,67]. Antimicrobial restorative materials have been developed through the incorporation of AgNPs to composite resins [23] and adhesive systems [68], for the prevention or the decrease of biofilm formation over composite and in the restorations margins.

Silver has also been incorporated into glass ionomer cements in order to improve the antibacterial properties, including compressive tensile strength and creep resistance. Sometimes, silver nanofibers have been attached to the implant surfaces for their activity against plaque biofilm and to decrease the need for high doses of antibiotics. In the treatment of periodontal pockets, intrasulcular injection of AgNPs has led to a clear improvement in clinical parameters and decline of microbial infection, AgNPs being as effective as application of tetracycline films in therapy of periodontal pockets [69].

For the prevention of denture stomatitis, AgNPs have been incorporated into polymers used as tissue conditioners and as denture base [70]. Some studies introduced AgNPs in endodontic materials, as nanosilver-gutta-percha to improve the antibacterial effect of gutta-percha [71], AgNPs irrigant solution for disinfecting the root canal system or AgNPs-containing mineral trioxide aggregate (MTA) [61], an important endodontic material used for perforations sealing, external/internal root resorption repair, and apexification.

In order to prevent biofilm accumulation over Titanium implants surface, AgNPs have been incorporated to implant surface, due to long-term antibacterial activity through controlling Ag release [62,63].

The adequate use in daily dental practice of the multiple benefits and opportunities conferred by silver nanotechnology may be a significant adjunct for the prevention and treatment of dental disorders, leading to the improvement of oral health. However, extensive research is needed to evaluate the risk and the toxicity of silver nanostructured materials, as well as cost effectiveness and patient acceptance [70,72]. Further studies are also needed to determine the long term effects of the AgNP containing dental materials, the best ways of silver incorporation, the optimal concentration of AgNPs and its release over time, as well as the possible negative influence in dental materials, especially regarding color changes and mechanical properties [69].

4. CONCLUSIONS

In evolving formulations, the silver has been a constant element in local treatment and has acquired a well definite place in the wound care armamentarium. The role of silver is specially increasing in burns management, keeping in mind the susceptibility of burn lesions to localized and spreading infection, which can determine multiple local and systemic deleterious effects. In present times of bacterial multi-resistance to antibiotics, the irrefutable indication of silver in burns, either infected or with high risk of infection, is based on the very broad-spectrum anti-infectious properties, including anti-biofilm activity, and on the significantly low bacterial resistance. In burns management, the application of silver should be made after the carefully assessment of the whole patient and of the burn wounds and should accompany other therapeutic measures addressed to local and general repercussions of thermal aggression. Among these measures, wound bed preparation and the need for surgery have a decisive impact on prophylaxis and treatment of infection and on wound healing. As evidenced by studies and clinical trials, modern silver containing dressing have better healing outcomes compared to SSD and should be used instead of SSD, whenever possible. In addition to anti-infectious activity, silver dressings have revealed other favorable effects for wound healing, especially in clinical experience. However, due to the conflicting evidence of some studies targeting potential silver cytotoxicity, the silver dressings should be reserved for use in burn wounds with or at risk of local infection and should be discontinued when the signs and symptoms of wound infection have disappeared, the wound has improved and the beginning of epithelialization has occurred. Although AgNPs have been shown to be biocompatible with mammalian cells, further studies are needed to assess the Ag optimal concentration and way of incorporation, as well as the long-term properties of the new very promising AgNP-containing dental materials.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Alexander W. History of the medical use of silver. Surgical Infections. 2009;10(3):289-92.
2. Dunn PM. Dr Carl Credé (1819–1892) and the prevention of ophthalmia neonatorum. Arch Dis Child Fetal Neonatal. 2000;83: 158-159
3. Klasen HJ. Historical review of the use of silver in the treatment of burns. I. Early uses. Burns. 2000;26:117-30.
4. Powell J. Our mightiest germ fighter. Sci Dig. 1978;56-60.
5. Atiyeh BS, Costagliola M, Hayek SN, Dibo SA. Effect of silver on burn wound infection control and healing: Review of the literature. Burns. 2007;33(2):139-48.
6. Yabanoglu H, Basaran O, Aydogan C, Azap OK, Karakayali F, Moray G. Assessment of the effectiveness of silver-coated dressing, chlorhexidine acetate (0.5%), citric acid (3%), and silver sulfadiazine (1%) for topical antibacterial effects against the multi-drug resistant *Pseudomonas aeruginosa* infecting full-skin thickness burn wounds on rats. Int Surg. 2013;98(4):416-23.
7. Percival SL, Thomas J, Linton S, Okel T, Corum L, Slone W. The antimicrobial efficacy of silver on antibiotic-resistant bacteria isolated from burn wounds. Int Wound J. 2012;9(5):488-93.
8. Sim W, Barnard RT, Blaskovich MAT, Ziora ZM. Antimicrobial silver in medicinal and consumer applications: A patent review of the past decade (2007-2017). Antibiotics (Basel). 2018;7(4):93.
9. Percival SL, Woods E, Nutekpor M, Bowler P, Radford A, Cochrane C. Prevalence of silver resistance in bacteria isolated from diabetic foot ulcers and efficacy of silver-containing wound dressings. Ostomy Wound Manage. 2008;54(3):30-40.
10. Frazer RA. Use of silver nanoparticles in HIV treatment protocols: A research proposal. J Nanomedic Nanotechnol. 2012;3:1.
11. Ghiuță I, Cristea D. Silver nanoparticles for delivery purposes. Nanoengineered Biomaterials for Advanced Drug Delivery. 2020;347-371.
DOI: 10.1016/B978-0-08-102985-5.00015-2
12. Morones JR, Elechiguerra JL, Camacho A, Holt K, Kouri JB, Ramírez JT, Yacaman MJ. The bactericidal effect of silver nanoparticles. Nanotechnology. 2005;16: 2346.
13. Cooper R. A review of the evidence for the use of topical antimicrobial agents in wound care. World Wide Wounds; 2004.

14. Murphy PS, Evans GR. Advances in wound healing: A review of current wound healing products. Plast Surg Int. 2012; 190436.
DOI: 10.1155/2012/190436
15. Burdușel AC, Gherasim O, Grumezescu AM, Mogoantă L, Ficai A, Andronescu E. Biomedical applications of silver nanoparticles: An up-to-date overview. Nanomaterials (Basel). 2018;8(9):681.
16. Chaw KC, Manimaran M, Tay FE. Role of silver ions in destabilization of intermolecular adhesion forces measured by atomic force microscopy in *Staphylococcus epidermidis* biofilms. Antimicrob Agents Chemother. 2005; 49(12):4853-9.
17. Kalishwaralal K, Barath Mani Kanth S, Pandian SR, Deepak V, Gurunathan S. Silver nanoparticles impede the biofilm formation by *Pseudomonas aeruginosa* and *Staphylococcus epidermidis*. Colloids Surf B Biointerfaces. 2010;79(2):340-4.
DOI: 10.1016/j.colsurfb.2010.04.014
18. Martinez-Gutierrez F, Boegli L, Agostinho A, Sánchez EM, Bach H, Ruiz F, James G. Anti-biofilm activity of silver nanoparticles against different microorganisms. Biofouling. 2013;29(6):651-60.
DOI: 10.1080/08927014.2013.794225
19. Goggin R, Jardeleza C, Wormald PJ, Vreugde S. Colloidal silver: A novel treatment for *Staphylococcus aureus* biofilms? Int Forum Allergy Rhinol. 2014; 4(3):171-5.
20. Warriner R, Burrell R. Infection and the chronic wound: A focus on silver. Adv Skin Wound Care. 2005;18(8):2–12.
21. Wong KK, Cheung SO, Huang L, Niu J, Tao C, Ho CM, Che CM, Tam PK. Further evidence of the anti-inflammatory effects of silver nanoparticles. ChemMedChem. 2009;4(7):1129-35.
22. Nadworny PL, Wang J, Tredget EE, Burrell RE. Anti-inflammatory activity of nanocrystalline silver in a porcine contact dermatitis model. Nanomedicine. 2008; 4(3):241-51.
23. Nadworny PL, Wang J, Tredget EE, Burrell RE. Anti-inflammatory activity of nanocrystalline silver-derived solutions in porcine contact dermatitis. J Inflamm (Lond). 2010;7:13.
24. Murphy PS, Evans GRD. Advances in wound healing: A review of current wound healing products. Plast Surg Int. 2012; 190436.
25. Fung MC, Bowen DL. Silver products for medical indications: Risk-benefit assessment. Clinical Toxicology. 1996; 34(I):119-26.
26. Thomas S, McCubbin P. An *in vitro* analysis of the antimicrobial properties of 10 silver containing dressings. J Wound Care. 2003;12(8):305-08.
27. Thomas S, McCubbin P. A comparison of the antimicrobial effects of four silver-containing dressings on three organisms. J Wound Care. 2003;12(3):101-7.
28. Yarboro DD. A comparative study of the dressings silver sulfadiazine and aquacel ag in the management of superficial partial-thickness burns. Adv Skin Wound Care. 2013;26(6):259-62.
29. Muangman P, Pundee C, Opasanon S, Muangman S. A prospective, randomized trial of silver containing hydrofiber dressing versus 1% silver sulfadiazine for the treatment of partial thickness burns. Int Wound J. 2010;7(4):271-6.
30. Lo SF, Hayter M, Chang CJ, Hu WY, Lee LL. A systematic review of silver-releasing dressings in the management of infected chronic wounds. J Clin Nurs. 2008;17(15): 1973-85.
31. Khundkar R, Malic C, Burge T. Use of Acticoat dressings in burns: What is the evidence? Burns. 2010;36(6):751–8.
32. Huang Y, Li X, Liao Z, et al. A randomized comparative trial between Acticoat and SD-Ag in the treatment of residual burn wounds, including safety analysis. Burns. 2007;33(2):161–6.
33. 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.
34. Verbelen J, Hoeksema H, Heyneman A, Monstrey S. Aquacel® Ag dressing versus Acticoat™ dressing in partial thickness burns: A prospective, randomized, controlled study in 100 patients. Part 1: Burn wound healing. Burns. 2014;40(3): 416-27.
35. Ding X, Shi L, Liu C, Sun B. A randomized comparison study of aquacel Ag and alginate silver as skin graft donor site dressings. Burns. 2013;39(8):1547-50.
36. Naiem S, Moiemen NS, Shale E, Drysdale KJ, Smith G, Wilson YT, Papini R. Acticoat dressings and major burns: Systemic silver absorption. Burns. 2011;37:27-35.

37. Sibbald RG, Goodman L, Krasner DL, et al. Special considerations in wound bed preparation 2011: An update. Adv Skin Wound Care. 2011;415-36.
38. Leaper D. Appropriate use of silver dressings in wounds: International consensus document. Int Wound J. 2012; 9(5):461-4.
39. Hermans MH. Silver-containing dressings and the need for evidence. Adv Skin Wound Care. 2007;20(3):166-73.
40. Drosou A, Falabella A, Kirsner RS. Antiseptics on wounds: An area of controversy. Wounds. 2003;15(5):149-66.
41. Hiro ME, Pierpont YN, Ko F, Wright TE, Robson MC, Payne WG. Comparative evaluation of silver-containing antimicrobial dressings on *in vitro* and *in vivo* processes of wound healing. Eplasty. 2012;12:48.
42. Lam PK, Chan ESY, Ho WS, Liew CT. *In vitro* cytotoxicity testing of a nanocrystalline silver dressing (Acticoat) on cultured keratinocytes. Br J Biomed Sci. 2004;61(3):125–7.
43. Paddle-Ledinek JE, Nasa Z, Cleland HJ. Effect of different wound dressings on cell viability and proliferation. Plast Reconstr Surg. 2006;117(7):110–118.
44. Poon VKM, Burd A. *In vitro* cytotoxicity of silver: implication for clinical wound care. Burns. 2006;30:140–7.
45. Burd A, Kwok CH, Hung SC, Chan HS, Gu H, Lam WK, et al. A comparative study of the cytotoxicity of silver-based dressings in monolayer cell, tissue explant, and animal models. Wound Rep Regen. 2007;15:94–104.
46. Leaper D, Drake R. Should one size fit all? An overview and critique of the VULCAN study on silver dressings. Internat Wound J. 2011;8:1–4.
47. Tian J, Wong KK, Ho CM, Lok CN, Yu WY, Che CM, et al. Topical delivery of silver nanoparticles promotes wound healing. Chem Med Chem. 2007;2(1):129-136.
48. Khansa I, Schoenbrunner AR, Kraft CT, Janis JE. Silver in wound care-friend or foe?: A comprehensive review. Plast Reconstr Surg Glob Open. 2019;7(8):2390. DOI: 10.1097/GOX.0000000000002390
49. Singh SP, Bhargava CS, Dubey V, Mishra A, Singh Y. Silver nanoparticles: Biomedical applications, toxicity, and safety issues. International Journal of Research in Pharmacy and Pharmaceutical Sciences. 2017;2(4):1-10.
50. Verdú Soriano J, Rueda López J, Martinez Cuervo F, Soldevilla Agreda J. Effects of an activated charcoal silver dressing on chronic wounds with no clinical signs of infection. J Wound Care. 2004;13(10):419-23.
51. Trial C, Darbas H, Lavigne JP, Sotto A, Simoneau G, Tillet Y, Téot L. Assessment of the antimicrobial effectiveness of a new silver alginate wound dressing: A RCT. J Wound Care. 2010;19(1):20-26.
52. Lazareth I, Meaume S, Sigal-Grinberg ML, et al. The role of a silver releasing lipido-colloid contact layer in venous leg ulcers presenting inflammatory signs suggesting heavy bacterial colonization: Results of a randomized controlled study. Wounds. 2008;20(6):158-66.
53. Khundkar R, Malic C, Burge T. Use of Acticoat dressings in burns: What is the evidence? Burns. 2010;36(6):751-8.
54. Jurczak F, Dugré T, Johnstone A, Offori T, Vujovic Z, Hollander D. AQUACEL Ag surgical/trauma wound study group. randomised clinical trial of hydrofiber dressing with silver versus povidone-iodine gauze in the management of open surgical and traumatic wounds. Int Wound J. 2007; 4(1):66-76.
55. Caruso DM, Foster KN, Blome-Eberwein SA, Twomey JA, Herndon DN, Luterman A, Silverstein P, Antimarino JR, Bauer GJ. Randomized clinical study of hydrofiber dressing with silver or silver sulfadiazine in the management of partial-thickness burns. J Burn Care Res. 2006;27(3):298-309.
56. Opasanon S, Muangman P, Namviriyachote N. Clinical effectiveness of alginate silver dressing in outpatient management of partial-thickness burns. Int Wound J. 2010;7(6):467-71.
57. Huang Y, Li X, Liao Z, Zhang G, Liu Q, Tang J, et al. A randomized comparative trial between Acticoat and SD-Ag in the treatment of residual burn wounds, including safety analysis. Burns. 2007; 33(2):161-6.
58. Wasiak J, Cleland H, Campbell F, Spinks A. Dressings for superficial and partial thickness burns. Cochrane Database of Systematic Reviews. 2013:3. Art. No.: CD002106.
59. Paddock HN, Fabia R, Giles S, Hayes J, Lowell W, Adams D, Besner GE. A silver-impregnated antimicrobial dressing

reduces hospital costs for pediatric burn patients. J Pediatr Surg. 2007;42(1):211-3.
60. Saba SC, Tsai R, Glat P. Clinical evaluation comparing the efficacy of AQUACEL Ag hydrofiber dressing versus petrolatum gauze with antibiotic ointment in partial thickness burns in a pediatric burn center. J Burn Care Res. 2009;30: 380-85.
61. Morones-Ramirez JR, Winkler JA, Spina CS, Collins JJ. Silver enhances antibiotic activity against gram-negative bacteria. Sci Transl Med. 2013;190(5):190ra81.
62. Corrêa JM, Mori M, Sanches HL, Cruz AD, Poiate E, Poiate IA. Silver nanoparticles in dental biomaterials. Int J Biomater. 2015; 485275.
DOI: 10.1155/2015/485275
63. Pokrowiecki R, Zaręba T, Szaraniec B, et al. *In vitro* studies of nanosilver-doped titanium implants for oral and maxillofacial surgery. Int J Nanomedicine. 2017;12: 4285-97.
DOI: 10.2147/IJN.S131163
64. Yin IX, Zhang J, Zhao IS, Mei ML, Li Q, Chu CH. The antibacterial mechanism of silver nanoparticles and its application in dentistry. Int J Nanomedicine. 2020;15: 2555-62.
65. Song W, Ge S. Application of antimicrobial nanoparticles in dentistry. Molecules. 2019;24(6):1033.
DOI: 10.3390/molecules24061033
66. Bapat RA, Chaubal TV, Joshi CP, Bapat PR, Choudhuri H, Pandey M, et al. An overview of application of silver nanoparticles for biomaterials in dentistry. Mater Sci Eng C Mater Biol Appl. 2018;91:881-98.
67. Lee D, Lee SJ, Moon JH, Kim JH, Heo DN, Bang JB, et al. Preparation of antibacterial chitosan membranes containing silver nanoparticles for dental barrier membrane applications. J Ind End Chem. 2018;66: 196-202.
68. Nowack B, Krug HF, Height M. 120 Years of nanosilver history: Implications for policy makers. Environ Sci Technol. 2011;45(4): 1177–83.
69. Desai C, Desai S. Silver nanoparticles in dental cure: Scenario and confronts. International Journal of Trend in Scientific Research and Development. 2018;2(2): 64-9.
70. Şuhani MF, Băciuţ G, Băciuţ M, Şuhani R, Bran S. Current perspectives regarding the application and incorporation of silver nanoparticles into dental biomaterials. Clujul Med. 2018;91(3):274-79.
71. Shantiaee Y, Maziar F, Dianat O, Mahjour F. Comparing microleakage in root canals obturated with nanosilver coated gutta-percha to standard gutta-percha by two different methods. Iranian Endodontic Journal. 2011;6(4): 140-5.
72. Takamiya AS, Monteiro DR, Bernabé DG, Gorup LF, Camargo ER, Gomes-Filho JE, et al. *In vitro* and *In vivo* toxicity evaluation of colloidal silver nanoparticles used in endodontic treatments. Journal of Endodontics. 2016;42(6):953-60.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/59312