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Antimicrobial and Anti-Inflammatory Properties of Silver Nanoparticles in BurnTreatment

Eric Yesaya[1], Anwar Lewa[2]

[1]General Practitioner, Krida Wacana Christian University, Jakarta, Indonesia

[2]Plastic Reconstructive and Aesthetic Surgery, dr.Esnawan Antariksa Air Force Hospital,Jakarta, Indonesia

ABSTRACT

Summary: Burn is one of the most common injuries which leading to high morbidity and mortality. Inflammation and infection involve in burn pathophysiology. Inflammation occurs in burn mainly due to release of inflammatory cytokines, while infection occurs when skin barrier damage and immune system is compromised due to suppression of neutrophils and T cells. In previous studies, silver nanoparticles (AgNPs) exhibit antimicrobial and anti- inflammatory properties through several mechanism. Antimicrobial mechanism of AgNPs including the damage of cell wall and alteration inner part of cell, while anti-inflammatory mechanism of AgNPs is by reducing pro-inflammatory cytokines. Therefore, silver nanoparticles can be reasonable treatment for burn.

KEYWORDS: Silver Nanoparticles, Burn, Antimicrobial, Anti-Inflammatory

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INTRODUCTION

Burn is an injury that is resulted by thermal, chemicals, electricity and radiation.[1] Burn is one of the most common injuries that leading to high morbidity and mortality.[2,3] The depth of the burn injury and the area ofbody surface affected determine the severity of burn injury. Burns damage skin barrier against bacteria. This condition can result vulnerability to infection. The injuries also generate moist environmentthat is ideal condition for bacteria to grow.[4]

Silver nanoparticles (AgNPs) are a nanomaterial that have a size between 1- 100 nm. In the bulk form, AgNPs exhibit larger capacity and higher surface than silver.[5] They still have bioactive characteristic of silver even in the form of nanoparticles. Furthermore, due to the size of nanoparticle, it benefits to varioussituation.[6] Unique electrical, optical, and catalytic feature of AgNPs have led to the investigation and manufacture of products for diagnosis, detection, and imaging.[5] AgNPs is one of the silver products that commonly used in modern medicine because of their physicochemical characteristic. AgNPs are commonly used as antimicrobial agent in medicine. The ability of AgNPs as antimicrobial are associated with molecule's binding surface.Small molecules like AgNPs present greater antimicrobial ability. They are effective against gram-negative and gram- positive bacteria. AgNPs exhibit antifungalability against like Candida albicans and Aspergillus niger. Previous studies about viruses have shown antiviral feature of AgNPs, including HIV, HBV, HSV, Influenza Virus, or SARS-CoV-2. AgNPs also provide anti-oxidative, anti-tumor, anti-angiogenic, and anti-inflammatoryeffects.[6]

BURN PATHOPHYSIOLOGY

Inflammation

Inflammation and infection process in burnis described in Figure 1. Initial response to the burn, immune cells like macrophages, monocytes, neutrophils, mast cells, dendritic cells (DCs) migrate to the site of injury.[7,8,9] They recognize damage- associated molecular patterns (DAMPs) and pathogen-associated molecular pattern molecules (PAMPs).[7,8] These molecules are recognize by pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs).[7,8,10] This causes the activation of NF-kB thus releaseof multiple cytokines like IL-1, IL-6, IL-8, IL-18 and TNF-α, which are inflammatory mediators.[7,10] Furthermore, thecontinuation of inflammation cycle due to release of these cytokines induce systemic inflammatory response syndrome (SIRS) thus resulting to multiple organ failure.[7,10]

Infection

Infection can occur when immune system is compromised mainly in burn injuries. Disruption of neutrophils which role to phagocytosis, create neutrophilextracellular traps (NETs) and reactive oxygen species (ROS), also suppression of T cell and IL-2 can lead to compromised immune system and vulnerability to infection.[7,8] Burn also damage the skin barrier allowing bacteria to colonize and grow in the areas of injury. The source of infection can originate from anywhere, such as from skin itself, from the hospital environment such as ventilator or intubation (related to pneumonia) and urinary catheters (related to urinary tract infection).[7,8,11,12]

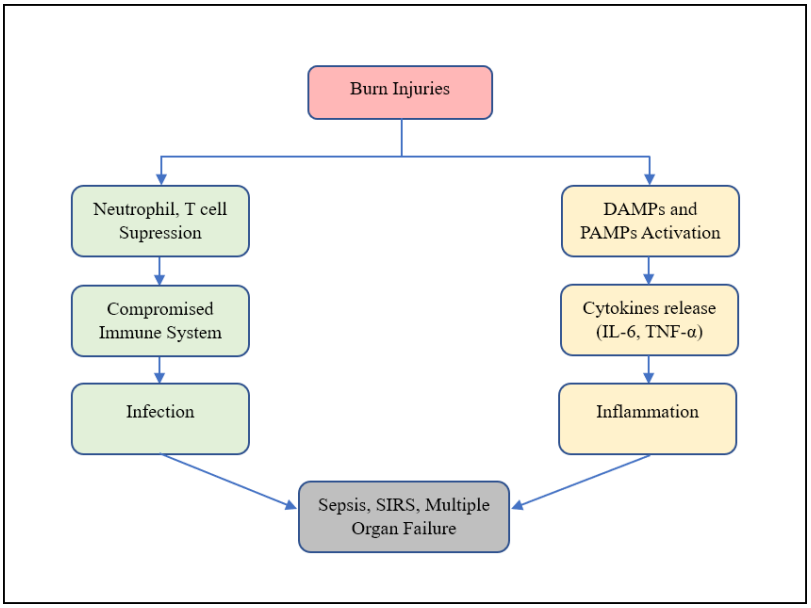

Figure 1. Inflamation and infection process in burn.

Activation of damage-associated molecular patterns (DAMPs) and pathogen-associated molecular pattern molecules (PAMPs) lead to the release of cytokine thus inflammation occurs. Supression of T cell and neutrophils lead to compromised immune system search of the cell membrane which containcarboxyl and phosphate. Therefore, AgNPscan attach to cell membrane. Cell wall alsoconsist of sulfur-containing proteins that can interact with silver nanoparticles. Theseresult structural change of cell membrane by disruption of lipid bilayer integrity, enhancement in permeability which cause disturbance of transport activity, leakage ofcellular contents and damage of cell wall.[5,6,13,14] Study on E. coli treated with AgNPs have shown that there is disruption of the outer membrane of E. coli, which is resulted from accumulation of immature membrane precursor proteins. Accumulation of immature membrane precursor proteins indicates dissipation of proton motive forces and reduction of cellular ATP, which cause disturbance of precursor protein translocation to the cell membrane.[14]

The second mechanism is alteration inner part of cell. Disulfide bridges which are enzymes of cellular metabolism and thiol

groups which are respiratory enzymes, are found in cell membranes, mitochondria andribosome. Silver ions bind to thiol groups (ASH), forming stable SAAg bonds. Interactions between them and silver ions leads to disruption of transmembrane transport of potassium ions, decreases the production of transmembrane ATP and creates reactive oxygen species (ROS) and cellular oxidative stress in cell. ROSoxidize the double bonds of fatty acids in the membrane, which result the productionof other free radicals. Silver ions interact with nucleic acids, causing disruption and mutations including DNA repair genes (mutY, mutS, mutM, mutT, and nth). Silveralso forms complexes with DNA. The ionsform complexes with nucleic acids,intercalate between the purine and pyrimidine base pairs and separate the H- bonds between antiparallel base pairs,therefore disrupts the double helical structure. Silver nanoparticles in the DNA helix may prevent the transcription of genes. DNA molecule's form shifts from the relaxed to condensed. This results to inhibition of proper transcription process and prevents bacteria from replication and multiplying. [6,13,14]

AgNPs also create another free radical species such as superoxide anion (O_2^-), hydrogen peroxide (H2O2), hypochlorous acid (HOCl), hydroxyl radical (OH^-) and singlet oxygen. Through one-electronreduction catalyzed by nicotinamide adenine dinucleotide phosphate (NADPH)

SILVER NANOPARTICLES IN BURN TREATMENT

Antimicrobial Properties in Silver Nanoparticles

As previously explained, burn injuries can compromise immune system which can lead to microbial infection. AgNPs are well known for its ability as antimicrobial against bacteria.[5,6,13,14,15,16,17] There are several antimicrobial mechanisms of AgNPs. The first mechanism is the damageof cell wall. Dissolution of silver nanoparticles result silver ions. Electrostatically, positively charge silver ions interact with negatively charged

oxidase, O_2 which is the primary ROS, is created by molecular oxygen. By dismutation and Fenton's reaction, further molecular oxygen reduction will create H_2O_2 or OH. More creation of free radicals results mitochondrial membranes damage that leads to necrosis. Hyperoxidation of lipids, proteins and DNA also happen from ROS enhancement. Lipids in biomembranes interact with free radicals to produce lipid peroxidation which involve in mutagenesis. The nanoparticles trigger genotoxicity, chromosome aberration, mutation, and DNA strands distortion. DNA components interact with hydroxyl radical (OH-) to generate 8-hydroxyl-2′-deoxyguanosine (8-OHdG) DNA adduct. This lead to DNA lesions and DNA single strand damage.[14]

Furthermore, silver interaction with ROS scavengers results in reduction of scavenging free radical activity andenhance oxidative stress. Glutathione(GSH) is one of the free radical scavengers. It is transformed by silver ions into inactive oxidized form (GSSG). These result disruption of antioxidant and free radical resistance in bacteria.[6] Silver ions bond with 30S ribosome subunit, which lead to inactive ribosome complex and cease protein synthesis and translation. Silver nanoparticles effect on ribosomes, transcription, and translation, resultsynthesis of immature precursor proteins in cell membrane formation, which result to cell death. Silver nanoparticles also disruptcellular metabolism by affecting enzymesuccinyl coenzyme-a-synthetase which isinvolved in tricarboxylic acid cycle. It was also suggested that silver nanoparticles interrupt RNA transcription, purines, pyrimidines, fatty acids of bacteria, and alter the gene expression. At the tier ofcytochrome oxidase and NADH-succinate dehydrogenase, silver nanoparticles block the respiratory chain.[13]

Previous study on E. coli treated with AgNPs exhibit the effluxes of aggregated phosphates, succinate, mannitol, glutamineand proline due to suppression of phosphateuptake and growth of E. coli by AgNPs. AgNPs also prevent oxidation of fumarate,succinate, glycerol and glucose in E. coli. Because of greater level in substantial surface zone they exhibit good bactericidal ability.[15] Study about nano silver dressing in burn treatment showed that the positive rate of wound secretion was significantly decreased after bacterial culture when usingnano silver burn dressing compared to using silver sulfadiazine cream.[16] Other studies showed that AgNPs hydrogelsbased were a potent alternative to silver sulfadiazine for healing of burn wound infections, without causing cytotoxicity.[17]

Anti-Inflammatory Properties in Silver Nanoparticles

Several studies showed anti-inflammatory properties in silver nanoparticles. AgNPs inhibit the expressions of COX-2 and MMP-3, also decrease TNF-α activity. In vivo, in the beginning of inflammation, pre- administration of AgNPs reduced edemaand cytokine levels in the tissues. In vitro, in the treatment of psoriasis, polyphenol- coated silver nanoparticles exhibit good anti-inflammatory property. They hinder the production of pro-inflammatorycytokines through preventing activation of NF-kB in macrophages.[13] A study also showed reduction of TNF-α and IL-1β levels significantly using nanosilver dressing in second-degree burn treatment.[14]

APPLICATION OF SILVER NANOPARTICLES IN BURN TREATMENT

AgNPs are applied in partial-thickness burn as wound dressing. After surgical debridement of the wound, AgNPs productis fixated with metallic sutures. With distilled water, the gauze dressing on the wound is moistened and changed weekly. The dressing is removed at around days 14.[18]

CONCLUSION

Silver nanoparticles act as antimicrobial through disruption of cell wall and alteration inner part of cell. They also have good anti-inflammatory properties by preventing the production of pro- inflammatory cytokines. Thus can prevent infection and inflammation that can lead toSIRS and multiple organ failure in burn.

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CONFLICT OF INTEREST

There is no conflict of interest

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