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REVIEW

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The use of nanoparticles in wound treatment: a systematic review

Utilização de nanopartículas no tratamento de feridas: revisão sistemática

Utilización de nanopartículas en el tratamiento de heridas: revisión sistemática

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ABSTRACT

Objective: To analyze the effects of nanoparticle-based dressings on the wound healing process in in vitro animals and human cells based on scientific evidence. **Method:** A systematic review of the literature in LILACS, PubMed and Science Direct databases. The articles were selected and evaluated for the level of evidence by the application of STROBE. **Results:** The sample consisted of 12 articles. The application of the products occurred in surgical wounds, burns, infected wounds and gingival ulcers in laboratory animals, as well as *in vitro* tests, demonstrating that among other advantages, the nanoparticle-based dressings increased the healing speed, had good antibacterial capacity and were non cytotoxic agents. **Conclusion:** Based on the analyzed articles, it can be affirmed that dressings containing nanocomposites are quite promising and are shown as a great therapeutic option in wound healing.

DESCRIPTORS

Wounds and Injuries; Nanoparticles; Wound Healing; Nursing Care; Review.

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INTRODUCTION

Chronic wounds in Brazil have been causing serious public health problems due to the large number of people with impaired skin integrity, difficulty in treatment, burdening public expenditures[1], as well as causing personal, social, psychological and economic harm. They are often difficult to treat because they are associated with comorbidities such as: diabetes mellitus, spinal cord trauma, malnutrition, vasculopathies, immunosuppression, autoimmune diseases, and psychiatric disorders, among others. This makes the treatment more challenging and as well as requiring nurses to have skills and knowledge[2], nurses must be able to use available resources and technologies to provide the most effective assistance while respecting the comfort of the patient.

Wound care and treatment is part of the nursing care routine and it is the responsibility of the nurse to plan and evaluate this care, and it must be done in a comprehensive and careful manner, taking the biopsychosocial aspects of the clients into account. However, given the diversity of variables involved in wound care and the active participation of the client and its family for effective treatment there must also be multiprofessional interaction.

It is known that the presence of a wound causes discomfort, and changes in the lifestyle and the psychological well-being of patients, especially in cases where there is impairment of self-image and denial of health status[3]. Thus, it is important to emphasize that the nurse must define the objective and draw up a plan of personalized care for each client, directed not only to the wound, but to the individual as a whole based on the nursing process.

Nowadays, there is a large arsenal of wound care products, which allows the nurse to choose the ideal one for each situation. These products have been undergoing scientific and technological advances over the years, with huge varieties that promote healing, including products aimed at protecting the skin from breakdown; "prevention of infections; hygiene and antisepsis products; products for chemical, enzymatic, autolytic or mechanical debridement; primary dressings (come in direct contact with the wound bed) or secondary (serve to fix the primary dressings); products for fixation of dressings and complements (bandages) and topical agents"[4]. The new products aim not only to accelerate the healing process, but also to reduce possible complications[4-5].

Nanotechnology which already has potential application recognized in aerospace engineering, nanoelectronics, medical health and consumer products, is also the result of these advances and is rapidly growing, they are particles or clusters with size distribution that present a considerable fraction of particles having one or more dimensions in the range of one to 100 nanometers (nm). An nm represents one billionth of a meter. The control of this manipulation, in the manometric scale, searches for properties and characteristics that could not be obtained otherwise[6].

Nanoparticles have been produced and used in a wide range of products worldwide, including silver nanoparticles (AgNP) and other compounds, such as nitric oxide and chitosan, which are promising in wound treatment[7].

Silver has always been used in the form of silver metal, silver nitrate, silver sulfadiazine for the treatment of wounds, burns and various bacterial infections. Nanotechnology is gaining tremendous momentum in the present century because of its ability to modulate metals by drastically changing their chemical, physical and optical properties. For example, metallic silver in the form of nanoparticles, made a remarkable return as a potent antimicrobial agent since the pathogenic bacteria developed resistance against several antibiotics[8].

Wound care has become a specialty within nursing, a challenge that requires specific knowledge, skill and a holistic approach. Until recently it was an area with few admirers, but nurses are now gradually identifying themselves and organizing a systematic and therapeutic approach to skin and wound care, achieving autonomy for the profession in this area[8]. Undoubtedly, this is a task performed by nursing in daily practice, making the nurse the most appropriate professional for the prevention, evaluation and treatment of wounds[9].

The need for constant updating of treatments and wound care was realized when the scope of the nurse's role in wound prevention and wound care is considered, this role includes the nursing consultation, prescription of medications/dressings and the request of inherent laboratory tests established in institutional programs or protocols, dressings, wound debridement, the use of scales for wound prevention and the use of technologies[10]. Nevertheless, literature searches have identified a lack of knowledge in the area, creating interest in researching the production of articles on the use of nanoparticles in the treatment of wounds, how it is being applied and the results achieved with its implementation, which has been promising and revolutionary in the treatment of wounds. Therefore, the objective of the study was to analyze the effect of nanoparticle-based dressings on the wound healing process in *in vitro* animals and human cells based on the scientific evidence.

METHOD

This is a systematic review of the literature, one of the many methodological resources used to integrate information from separate independent studies that work on the same thematic basis, producing concise syntheses on a specific issue, as it identifies, analyzes and gathers data on a particular subject[11-12].

The systematic review begins from an appropriate definition of the guiding question, known as the problem. At this moment, aspects directly related to the objective should be considered as participants, interventions should be evaluated, and outcomes measured[13].

For this to occur, PICO is used which refers to four important components for the formulation of a research question, where P = participant, I = intervention, C = control and O = outcome. Knowing at least two of them is mandatory, the participant (P) and intervention (I)[14].

The question that guided the systematic review of the literature in this study was: What is the effect of the use of nanoparticle-based dressings for wound healing in *in vitro* animal and human cells? Thus:

Chart 1 – PICO Strategy – Fortaleza, Ceará, Brazil, 2015.

P	Rats, rabbits, cells.
I	Nanoparticle-based dressings
O	Wound healing

Data collection was carried out from June to August in 2015. The study search was performed by two independent researchers, using the advanced search strategy in the periodicals portal of the Coordination for the Improvement of Higher Level Personnel (CAPES – *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior*) for searches in the electronic databases of the US National Library of Medicine National Institutes of Health (PubMed) and Science Direct, in which the following English descriptors were used: "wound", "dressing" and "nanoparticle", selected from the Medical Subject Headings (MeSH). The following descriptors in Portuguese were used for the searches in the Latin American and Caribbean Literature in Health Sciences database (LILACS): "*feridas*", "*curativos*" and "*nanopartículas*", from the Health Sciences Descriptors (DeCS – *Descritores em Ciências da Saúde*). The logical operator "AND" was used to combine the descriptors which were used to track the publications.

From prior reading of titles and abstracts 1,234 publications were initially identified, and 45 potentially eligible articles for inclusion in this review were pre-selected. Next, the articles that met the following inclusion criteria were identified: (a) the articles should be complete; (b) publication period from 2010 to 2015, due to the increased production of studies on the subject in recent years; (c) in Portuguese, English and Spanish. It was decided not to include review articles, theses, dissertations and monographs, seeking to contemplate a higher level of evidence. After thorough reading of the articles in full, articles that did not meet the guiding question were excluded. 12 articles were selected to be part of the discussion of this study.

Figure 1 shows in brief, how the selection process of the studies took place.

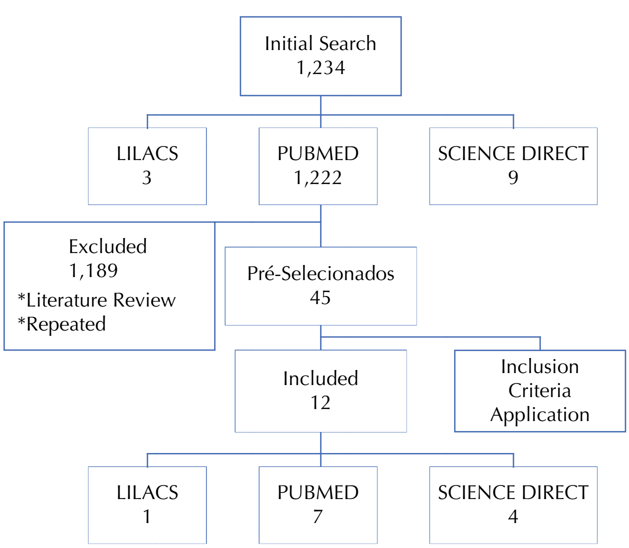

Figure 1 – Flowchart of the selection process of the included studies in the systematic review – Fortaleza, Ceará, Brazil, 2015.

An instrument was used to collect data from the articles, including bibliometric information (author/year, code, title, database and country), methodological details of the studies (study design, population/sample), intervention, application and outcome. The results were briefly presented in descriptive form, in three tables, which were discussed and compared to the action and results of the products and their contradictions.

The selected articles underwent an evaluation of the study design by the application of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) instrument, which consists of a checklist composed of 22 items with recommendations on what should be included in a more detailed and complete description of observational studies in order to indicate the level of evidence in the study[15].

RESULTS

Twelve articles were selected. According to the method employed, 1,234 potential researches were found from the search strategy, and most articles were obtained from the PubMed database, (99.10%), followed by Science Direct (0.72%) and LILACS (0.16%).

From the 12 resulting studies in the final sample, nine (75%) were found in PubMed, two (16.66%) in Science Direct and one (8.33%) in LILACS. Table 2 presents the synthesis of the studies containing the main results.

The studies were conducted in the following countries: Brazil, Saudi Arabia, Italy, India, Turkey, South Korea, Japan and Taiwan, with each contributing one study, the United States of America contributed two and China contributed three. The surveys were published between 2010 and 2015. English was the language found in all investigations.

As for the study design, clinical trial was prevalent, with a total of 11, one being randomized, the other being a pre-clinical trial. It was observed that, in relation to the products used, ten different types were found. From these ten different types, six dressings were based on silver nanoparticles, two being mixed with other products, and the other based on nanoparticles of other products (bacterial cellulose, nitric oxide, fibrin, lipid cyclosporine A, calcium, gentamicin) associated or not. Ten were used directly on the wound bed, while the other two were injected. From the studies in question, seven evaluated the use of the dressing in surgical wounds, three in burns, one in infected wounds and one in gingival ulcers. Eight of the 12 articles also performed in vitro tests, and most of them worked with human fibroblastic cells (Chart 3).

Regarding the outcome, 11 of these articles evaluated the speed of healing, which showed reduced time in all. Some studies also evaluated the antibiotic capacity, the hemostatic effect, the increase of fibroblast proliferation rate and the recruitment of angiogenesis factors.

After applying STROBE, which allowed a complete evaluation of the studies including the title, abstract, introduction, methodological detail, description of results and discussion, none of the studies presented agreement with all items of the evaluation of the researchers. However, all articles that composed the final sample of this systematic review answered at least 72% of the checklist items, indicating good methodological quality. Three of the articles answered 20 items, five answered 19 items, one answered 18 items, two answered 17 items and one answered 16 items (Chart 4).

Chart 2 – Synthesis of studies containing code, author / year, title and main results – Fortaleza, Ceará, Brazil, 2015.

CODE/ AUTHOR/ YEAR	TITLE	RESULTS
A1 Hendi 2010[16]	Silver nanoparticles mediate differential responses in some of liver and kidney functions during skin wound healing	Silver nanoparticles (AgNP) were injected intraperitoneally in rats with wounds, and it was found that the healing rate increased in animals treated with AgNP when compared to the control. It was found that the healed wound in the AgNP group showed greater resemblance to normal skin, with less hypertrophic scar and hair growth almost equal to the surface of the wound, with a thin epidermis and almost normal hair follicles.
A2 Rigo *et al.* 2013[17]	Active silver nanoparticles for wound healing	Silver nanoparticles were used, using the Acticoat™ Flex 3, with application of the product directly onto the wound bed, in a burn in a human, and showed a higher healing speed.
A3 Li *et al.* 2013[18]	Silver nanoparticle/ chitosan oligosaccharide/ poly(vinyl alcohol) nanofibers as wound dressings: a preclinical study	The use of pure *poly (vinyl alcohol)* (PVA)/*chitosan oligosaccharides* (COS), PVA/COS-Nitrate silver nanofibers (AgNO3) and PVA/COS-AgNP nanofibers were compared. In the evaluation of wound healing time, four full-thickness circular wounds were cut into the back of rats and covered with PVA/COS-AgNO3 nanofibers, PVA/COS-AgNP nanofibers, commercially available (positive control) coatings or gauze (negative control). Wound closure was observed in all treatment groups within 14 days. The results of the histological examination showed that healing was superior when using PVA/COS-AgNP nanofibers. Seven days after grafting, wounds in the groups with PVA/COS-AgNO3 nanofiber and gauze exhibited ulcerated surfaces, granulation tissue formation and infiltration of inflammatory cells, while the granulation tissue in the PVA/COS-AgNP nanofiber group disappeared without capillary hyperplasia.
A4 Wen *et al.* 2015[19]	In vitro and in vivo investigation of bacterial cellulose dressing containing uniform silver sulfadiazine nanoparticles for burn wound healing	Using bacterial cellulose dressings containing silver nanoparticles (BC-SSD), *in vitro* tests were performed to analyze the antibacterial action of BC-SSD and an excellent result was found against *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli*. *In vivo* tests were also performed using two groups of rats, the product was applied directly to the burn which was created for the study and a tendency of an increased bacteria count in the first four days for both groups was observed, but the amount of bacteria on the surface of the wound in the BC-SSD group in suspension was much lower than in the control group.
A5 Prestes *et al.* 2012[20]	Wound healing using ionic silver dressing and nanocrystalline silver dressing in rats	The rats were divided into three groups: the control group with distilled water (AD), Silver Ionic group (PI) and Silver Nanocrystalline (PN) group, surgical wounds were performed to analyze the contraction of the wound and the reduction of inflammation, observing the groups PI x AD and PN x AD for 21 days. The intensity of the inflammation was macroscopically analyzed, which on the seventh day was more pronounced in the AD and PI groups, in 90% of the cases. However, comparing the evaluation days, two by two, the AD and PN groups presented more statistically significant values. Regarding the histological analysis, it was demonstrated that there was no inflammation in any group, and the control group was superior to the PN and PI groups. Finally, in the analysis of the wound contraction, in relation to the delimited area of the surgical wound, it was observed that the PN and PI groups presented better results when compared to the AD group. Another relevant point was the presence of macrophages, already observed in the first week in the PN and PI groups, while in the same period there were no cases in the AD group.
A6 Chu *et al.* 2012[21]	Nanohybrids of silver particles immobilized on silicate platelet for infected wound healing	Six groups were tested. Nanoscale silicate platelets containing silver nanoparticles (AgNP/NSP) with a large surface area and high biocidal efficacy were developed, expressing a tendency of lower cytotoxicity and low genotoxicity, proving to be a great wound healing agent. AgNP/NSP cytotoxicity was analyzed in human foreskin fibroblasts and the indication of cytotoxicity was correlated directly to the dose used. Compared to other commercial drugs, AgNP/NSP showed a lower tendency to toxicity at a concentration of 8.75 ppm Ag. The pathogen *Staphylococcus aureus* (Staph) was used to promote wound infection. In the acute burn model, the wound area in the Staph + AgNP/NSP group was significantly lower than in any of the other groups, and six of them had significantly lower wound areas on days two, four and seven. Wounds treated with AQ or sulfadiazine (SS) also resulted in significantly smaller wound areas compared to untreated Staphylococci, Staph + NSP and Staph + Poly-Ag groups. However, on day seven, AQ did not show a smaller area when compared to the one treated with Staph + NSP. NSP treatment was significantly better than wound healing with Staphylococcus and Staph + Poly-Ag on days four and seven. A smaller wound area was observed in the poly-Ag group than in the untreated groups and in the Staphylococcus group on days four and seven.
A7 Karavana *et al.* 2012[22]	A new approach to the treatment of recurrent aphthous stomatitis with bioadhesive gels containing cyclosporine A solid lipid nanoparticles: in vivo/in vitro examinations	A gel formulation of Cyclosporine A loaded with solid lipid nanoparticles (NLS/CsA-loaded) was developed and applied *in vivo*. The observations were made in rabbits, divided into three groups, in which gingival ulcers were made for application and analysis of the product. Wound healing was established by scoring the wound healing rate on days three, six, nine and 12, in addition to histological observations. The results revealed that on days three, six and nine, the dimensions of the area of the first group (gel-treated) and the second group (treated with the NLS/CsA-loaded gel) were smaller than those of the control group. The group treated with the NLS/CsA-loaded gel showed a decrease in edema. On day 12, complete epithelization was observed in the treated groups, while in the control group incomplete epithelization was observed. The NLS/CsA-loaded bioadhesive gel formulation significantly increased the rate of mucosal repair.

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A8 Han *et al.* 2013[23]	Nitric oxide–releasing nanoparticles accelerate wound healing by promoting fibroblast migration and collagen deposition	The *in vitro* application of nitric oxide nanoparticles (NO-NP) to human fibroblast and *in vivo* in rats demonstrated that NO-NP stimulated the migration of fibroblasts and collagen to the wound area, which did not happen with the control group and the NP group. One day after the wound, the group of NO-NP-treated fibroblasts repopulated significantly 15% more than the other groups. Three days after the wound, the group of fibroblasts treated with NO-NP also showed a 15% improvement in wound closure when compared to the other groups. The evaluation of the genic expression of collagens types I and III in human fibroblasts showed that in the NO-NP group the increase was significant compared to the others. Rapid healing of the wound was observed, reaching full closure 12 days after surgery, unlike the other groups. As for wound angiogenesis, in the NO-NP treated group, wounds exhibited dense vascularization and, at about the seventh day, exhibited significantly higher concentrations of TGF growth factor in contrast to the other groups.
A9 Nurhasni *et al.* 2015[24]	Nitric oxide-releasing poly (lactic-co-glycolic acid)-polyethylenimine nanoparticles for prolonged nitric oxide release, antibacterial efficacy, and in vivo wound healing activity	Full-thickness wounds were performed on rats and then methicillin-resistant *Staphylococcus aureus* (MRSA) was used to develop an infection. The rats were divided into two groups: one treated with Nitric Oxide – Poly (Lactic Acid-Co-Glycolic) (PLGA) Polyethylenimine (PEI) NPs (Nanoparticles) NO/PPNPs and another without treatment (control). *In vivo* analysis performed with rats and *in vitro* with mammalian fibroblast showed that NO/PPNPs showed potent bactericidal efficacy against (MRSA) and *Pseudomonas aeruginosa* and showed to be able to bind to the surface of the bacteria, depending on the concentration. The analyses further showed that NO released from NO/PPNPs mediates bactericidal efficacy and is non-toxic to healthy fibroblast cells.
A10 Fan *et al.* 2013[25]	GNPs-CS/KGM as hemostatic first aid wound dressing with antibiotic effect: In vitro and in vivo study	The modified chitosan/glucomannan konjac (GNP-CS/KGM) film showed synergistic effects that helped to stop lesion bleeding, as well as showing good antibiotic capacity for the addition of gentamicin. In vitro studies to evaluate the antimicrobial activity of the modified GNP-CS/KGM film against *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas* revealed a strong inhibitory effect against the bacteria mentioned above, while the C75K25 film only had an inhibitory effect against *Staphylococcus aureus*.
A11 Kawai *et al.* 2011[26]	Calcium-based nanoparticles accelerate skin wound healing	After the wounds were made on rats, a single intravenous dose of calcium-based nanoparticles was administered and, within the first 24 hours, they were able to acutely decrease the size of the open wound via contracture, however, the healing rate was similar to that of the control group. When the topical application of the calcium nanoparticles to the wounds was performed, no significant alteration of the healing rate was observed. In the *in vitro* analysis, an increase of calcium absorption by the fibroblasts was observed. Nanoparticles also increased the rate of proliferation of fibroblasts. A fibroblast-populated collagen structure was created to determine the effects of cell contraction when treated with CNP.
A12 Kumar *et al.* 2013[27]	In vitro and in vivo evaluation of microporous chitosan hydrogel/ nanofibrin composite bandage for skin tissue regeneration	*In vivo* and *in vitro* tests were performed using nanoparticles of fibrin mixed with chitosan hydrogel (CFBs). The hemostatic potential of CFBs has been proven to enhance blood clotting. The CFBs incorporated with 1% and 2% of fibrin were compared with chitosan and only CFBs incorporated with 2% of fibrin showed a significant difference. When compared with Kaltostat, regardless of concentration, a significant difference in blood coagulation was observed. Experiments to evaluate cytotoxicity were performed on human umbilical vein endothelial cells (HUVEC) and the non-toxic nature of CFBs was demonstrated. *In vivo* studies were performed on rats and wound healing was observed in two weeks when treated with CFBs.

Chart 3 – Distribution of studies according to code, study design, population/sample, intervention, application and outcome – Fortaleza, Ceará, Brazil, 2015.

CODE.	STUDY DESIGN	POPULATION/SAMPLE	INTERVENTION	APPLICATION	OUTCOME
A1	Clinical trial	Rats (2 groups)	SILVER NANOPARTICLE (AgNP)	Intraperitoneal Injection	Higher healing speed; better aesthetic appearance
A2	Clinical trial	*in vitro* fibroblast culture *in vivo* 1 human	ACTICOAT FLEX 3	Dressings	Reduced healing time
A3	Preclinical randomized trial	Rabbits (2 groups) 12 rats (4 groups) Human fibroblast cell	PVA/COS-AgNP NANOFIBERS VERSUS PVA/COS/$AgNO_3$ NANOFIBERS	Dressings	Reduction of bacterial growth; increase healing speed
A4	Clinical trial	Rats (2 groups)	SILVER SULFADIAZIN WITH NANO AND MICROPARTICLES WITH BACTERIAL CELLULOSE	Membrane directly into the wound	Early progression of reepithelialization; antimicrobial activity; healing area more organized
A5	Clinical trial	60 rats (3 groups)	NANOCRYSTALLINE SILVER ACTCOAT 7 FLEX VERSUS IONIC SILVER MEPILEX AG	Dressings	Reduction of wound inflammation and contraction in less time

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A6	Clinical trial	*in vitro* human foreskin fibroblast *in vivo* rats (7 groups)	SILVER NANOPARTICLES SUPPORTED IN SILICON PLATELETS NANOMETRIC SCALE (AgNP/NSP) COMPARED TO SILVER SULFADIAZINE AND AQUACEL	Dressings	Greater reduction of area burned in the same period; better therapeutic effect, revealing a clean environment
A7	Clinical trial	*in vivo* 36 rabbits (3 groups) *in vitro* cells of the oral mucosa of cow	CYCLOSPORINE A SOLID LIPID NANOPARTICLES (CSASLNS)	Oral bio adhesive gel	High rate of mucosal tissue repair
A8	Clinical trial	*in vitro* human fibroblasts *in vivo* rats (non-explicit group)	NO-NP (NITROGEN OXIDE NANOPARTICLES)	Applied topical suspension covered with occlusive dressing	Less healing time; recruitment of angiogenesis factors
A9	Clinical trial	*in vivo* rats *in vitro* mammalian fibroblasts (non-explicit group)	NO/PPNPS (NITRIC OXIDE – POLY (LACTICAL -CO-GLYCOLIC ACID) (PLGA) POLYETHYLAMINE (PEI) NPS (NANOPARTICULE)	Topical application with sterile gauze dressing	Powerful bactericide; accelerates epithelialization (significant reduction of wound area)
A10	Randomized clinical trial	*in vitro* *in vivo* rats (5 groups)	CHITOSAN/GLUCOMANNAN KONJAC (CS/KGM) INCORPORATED FILM WITH GENTAMICIN POLY NANOPARTICLES (DEX-GMA/AAC) (GNP-CS/KGM FILM	Mixed films and gauze	Effective hemostatic effect; good antibiotic capacity
A11	Clinical trial	*in vitro* e *in vivo* rats (non-explicit group)	CALCIUM-BASED NANOPARTICLES	Intravenous and topical administration	Reduces wound size by contracture; increases the rate of proliferation of fibroblasts
A12	Clinical trial	*in vitro* umbilical vein and fibroblast endothelial cells rats (4 groups)	MIXED FIBRIN NANOPARTICLES WITH HYDROGEL OF CHITOSAN (CFBs)	Dressings	Potentiated blood clotting and platelet activity

Chart 4 – STROBE score of selected articles in this review – Fortaleza, Ceará, Brazil, 2015.

CODE	TITLE	STROBE
A1	Silver nanoparticles mediate differential responses in some of liver and kidney functions during skin wound healing	19 items
A2	Active silver nanoparticles for wound healing	19 items
A3	Silver nanoparticle/chitosan oligosaccharide/poly (vinyl alcohol) nanofibers as wound dressings: a preclinical study	19 items
A4	In vitro and in vivo investigation of bacterial cellulose dressing containing uniform silver sulfadiazine nanoparticles for burn wound healing	19 items
A5	Wound healing using ionic silver dressing and nanocrystalline silver dressing in rats	18 items
A6	Nanohybrids of silver particles immobilized on silicate platelet for infected wound healing	20 items
A7	A new approach to the treatment of recurrent aphthous stomatitis with bioadhesive gels containing cyclosporine A solid lipid nanoparticles: in vivo/in vitro examinations	19 items
A8	Nitric oxide – releasing nanoparticles accelerate wound healing by promoting fibroblast migration and collagen deposition	17 items
A9	Nitric oxide – releasing poly (lactic-co-glycolic acid) – polyethylenimine nanoparticles for prolonged nitric oxide release, antibacterial efficacy, and in vivo wound healing activity	20 items
A10	GNPs – CS/KGM as hemostatic first aid wound dressing with antibiotic effect: in vitro and in vivo study	17 items
A11	Calcium – based nanoparticles accelerate skin wound healing	16 items
A12	In vitro and in vivo evaluation of microporous chitosan hydrogel/nanofibrin composite bandage for skin tissue regeneration	20 items

DISCUSSION

Among the articles analyzed, six used dressings based on silver nanoparticles (AgNP). For many years silver has been used as a dressing because of its antimicrobial capacity. Nowadays, silver-based dressings are quite popular, which can be composite, associated with a salt or elemental in the form of a nanoparticle, conferring this and other benefits.

In study A1, the use of intraperitoneal silver nanoparticles, applied in rats with wounds, increased the speed of healing and resulted in a better aesthetic appearance of the wounds[16]. A similar effect in healing was obtained in study A2 with the application of the product directly to the wound bed in a human burn. The results of this study were reinforced by the clinical observations of the Plastic Reconstructive Surgery Division of Padua and were consistent with data reported by other authors cited in this study who demonstrated how AgNP-based dressings are effective in reducing the time required for reepithelization and the lesser graft requirement compared to other treatments[17].

In study A3, a pre-clinical trial confirmed that the PVA/COS-AgNP nanofibers accelerated the wound healing rate in relation to the control group (gaze). During the first seven days, the PVA/COS-AgNP nanofibers allowed better healing of wounds. One possible cause may be the rapid and constant release of AgNP and the excellent antibacterial capacity of PVA/COS-AgNP[18] nanofibers.

Nanoparticles have shown to have many benefits for wound healing. However, the cytotoxicity of these products is of great relevance in order to make them suitable for human use, thus becoming a focus for studies involving products with nanoparticles.

In study A3, various concentrations of the products were used in human skin fibroblasts and when compared to the control, significantly decreased cell viability was identified when fibroblasts were incubated at higher concentrations (0.8-1.0 mg/ml) of the extraction medium from PVA/COS-AgNO3 nanofibers. Nevertheless, no significant cytotoxicity was observed at any concentration with the pure PVA/COS and with the PVA/COS-AgNP nanofibers[18].

However, although many studies analyze the cytotoxicity of the product and assure the absence or low cytotoxicity by testing, it is important to note that they were done *in vitro* under conditions quite different from those found in a wound, and therefore, should be considered that the effect observed *in vitro* may not correspond directly to the real situation. Many factors can interfere with the action of silver in *in vivo* tests, such as the possible presence of exudate anions, proteins and biofilms. Clinically, the tolerance to cytotoxicity is greater than that observed in in vitro systems both from a cellular and biochemical point of view[28].

In addition, study A3 indicated the acceptability of PVA/COS-AgNP nanofibers for transdermal drug administration and important antibacterial activity, significantly inhibiting the growth of *Escherichia coli* and *Staphylococcus aureus* bacteria[18].

Among some factors that interfere with healing, there is infection, which slows or prevents healing from happening. Therefore, the existence of dressings based on materials that guarantee the antibacterial action and tests that prove its effectiveness are necessary. In large burns the metabolism is altered due to the systemic inflammatory reaction, which can lead to infection of the burned area which in turn compromises healing. The application of silver nanoparticle dressings has shown to promote a proper environment for reepithelization, proving to be effective in the prevention and treatment of contaminated areas[29].

Some studies show results that reinforce this antibacterial action of dressings containing silver nanoparticles. In study A4, the use of silver nanoparticle-containing bacterial cellulose (BC-SSD) showed excellent results against *Staphylococcus aureus, Pseudomonas aeruginosa* and *Escherichia coli*, as well as high efficacy of BC-SSD suspended in partial thickness burn healing[19].

In study A5, researchers performed tests on ionic silver (PI) and silver nanocrystalline (PN) impregnated occlusive dressings in rats and reinforced the results of the articles discussed here, considering that there was a better contraction of the wounds in the PN and PI groups when compared to group AD, in addition to the presence of macrophages, already observed in the first week in the PN and PI groups. Macrophages are important in the healing process because they secrete proteases, release vasoactive substances, and growth factors that control cell proliferation. The efficacy of silver dressings on uninfected wounds was also demonstrated, showing that there was an improvement in healing in PI and PN groups, compared to the control group (AD), contrary to the results of another author cited in their studies[20].

In the A6 study, the use of silver nanoparticle-containing silicate platelets (AgNP/NSP) supported the presented evidence and indicated favorable results, such as reduction of wound area, lower cytotoxicity, low genotoxicity and better therapeutic effect in infection control, showing great wound healing abilities[21].

The articles found by this systematic review were not restricted to the research of products based on silver nanoparticles. With the use of this nanotechnology, other products are also being studied at nanometer scale for the development of new promising dressings, as explained below.

In study A7, when compared to the control group, the use of Ciclosporin A gel with solid lipid nanoparticles (NLS/CsA-loaded) showed a reduction in the oral wound area and significantly increased the rate of mucosal repair[22].

The increase in healing speed was also analyzed in study A8, in which a nitric oxide nanoparticle (NO-NP) dressing was used. When this product was applied in *in vitro* to human fibroblasts and in *in vivo* rats, increased collagen deposition during wound healing, rapid progression of wound closure, and improved angiogenesis rates was observed[23].

The combined data suggest that NO-NP improves wound healing, facilitates cell migration and collagen deposition. Thus, Nitric Oxide associated with nanoparticles has been shown to be an important product for wound healing in several aspects. As observed in study A8, it increases the speed of healing and the recruitment of angiogenic factors[23].

In another study, A9, the benefits of epithelization acceleration and its bactericidal capacity were evaluated. The *in vivo* analyses were carried out with rats and *in vitro* analyses with mammalian fibroblast using Polycyclic Acid Nitric Oxide (PLGA) Polyethylamine (PEI) NPs (Nanoparticles) (NO/PPNPs) with bactericidal action of NO/PPNPs being proven against methicillin resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*[24], as highlighted in other studies using nanoparticles[19,21].

The control group presented edema, ulceration and abundance of mononuclear inflammatory cells with deep inflammatory infiltrate, while the NO/PPNP treated group showed increased fibroblast-like numbers and decreased mononuclear inflammatory cells with healed skin structures similar to healthy epidermis. Thus, this study has shown that NO/PPNPs accelerates wound healing and epithelialization in MRSA-infected wounds. Therefore, wound healing, using this product, can be attributed both to the bactericidal effect and the favoring of wound healing by NO[24].

Other authors were also interested in studying the bactericidal action, according to study A10, which analyzed products as chitosan/glucomannan konjac (GNP-CS/KGM) film, incorporated with gentamicin poly (dex-GMA/AAC) nanoparticles, which identified good antibiotic capacity, as well as a hemostatic effect, shortening the bleeding time and significantly reducing the volume in relation to the control group[25].

Study A11 evaluated the effect of calcium nanoparticles (CNP) on wound healing in rats in topical and intravascular use. In the *in vitro* analysis of these nanoparticles, an increase in calcium absorption of the fibroblasts and an increase in the proliferation rate of fibroblasts was observed[26].

Finally, the results of study A12, performed using chitosan hydrogel mixed fibrin nanoparticles (CFBs), through *in vivo* and *in vitro* tests, reinforced the evidence of the contribution of the use of nanoparticle-based products to accelerate the process of blood coagulation, promotion of platelet activation and wound healing[27].

The advantage of using fibrin in nanoformulation is due to the ideal biomimetic matrix, in which the active portions of fibrin are ready for platelet activation, thus inducing a rapid healing process[27].

At the end of this discussion, the results of the studies suggest evidence that nanoparticle-based dressings are effective and beneficial.

The nurse, as the health professional who is mostly involved in the care of the wounded patient, should always be up to date regarding new available technologies for the treatment of wounds, seeking dressings solutions that guarantee the best recovery of the wounds and prevention of complications, providing greater comfort and quality of life for the patient, in addition to participating in the institutional decisions for the acquisition and indication of products, while considering their efficacy and patient safety.

It should be noted that, in general, the studies included in this review are incipient, considering that most are restricted to experimental phases of the research, because when searching the databases used for this Systematic Review, it was difficult to find applications in human beings. Therefore, new studies in clinical practice are needed to validate and make products involving nanoparticles available which will limit the generalization of the results.

The restrictions of the publication period of the studies and the databases used in the search strategy used are considered as limitations of this systematic review

CONCLUSION

Based on the analyzed articles, it can be stated that dressings containing nanocomposites are very promising and are an excellent therapeutic option in wound healing. Higher healing speed, wound contraction reduction, hemostatic effect, bactericidal action, low cytotoxicity, among others, were the results achieved and/or confirmed in the studies.

Although it has been demonstrated in this systematic review that nanoparticle-based products have relevant advantages in wound treatment, there has been a lack of research on human beings, highlighting the indication of new studies for application in clinical practice with safety.

RESUMO

Objetivo: Analisar, com base nas evidências científicas, os efeitos dos curativos à base de nanopartículas no processo de cicatrização de feridas em animais e células humanas *in vitro*. **Método:** Revisão sistemática da literatura realizada nas bases de dados LILACS, PubMed e Science Direct. Os artigos foram selecionados e avaliados quanto ao nível de evidência pela aplicação do STROBE. **Resultados:** A amostra foi composta por 12 artigos. A aplicação dos produtos se deu em feridas cirúrgicas, queimaduras, feridas infectadas e úlceras gengivais em animais de laboratório, além de alguns testes *in vitro*, demonstrando que os curativos à base de nanopartículas aumentaram a velocidade de cicatrização, possuíam boa capacidade antibacteriana e não eram citotóxicos, dentre outras vantagens. **Conclusão:** Tomando por base os artigos analisados, pode-se afirmar que os curativos contendo nanocompostos são bastante promissores e mostram-se como uma ótima opção terapêutica na cicatrização de feridas.

DESCRITORES

Ferimentos e Lesões; Nanopartículas; Cicatrização; Cuidados de Enfermagem; Revisão.

RESUMEN

Objetivo: Analizar, con fundamento en las evidencias científicas, los efectos de los apósitos a base de nanopartículas en el proceso de cicatrización de heridas en animales y células humanas *in vitro*. **Método:** Revisión sistemática de la literatura realizada en las bases de datos LILACS, PubMed y Science Direct. Los artículos fueron seleccionados y evaluados en cuanto al nivel de evidencia por la aplicación del STROBE. **Resultados:** La muestra estuvo compuesta de 12 artículos. La aplicación de los productos se dio en heridas quirúrgicas, quemaduras, heridas infectadas y úlceras en la encía en animales de laboratorio, además de algunas pruebas *in vitro*, demostrando que los apósitos a base de nanopartículas aumentaron la velocidad de cicatrización, tenían buena capacidad antibacteriana y no eran citotóxicos, entre otras ventajas. **Conclusión:** Tomando como base los artículos analizados, se puede afirmar que los apósitos conteniendo nanocompuestos son bastante prometedores y se muestran como una excelente opción terapéutica en la cicatrización de heridas.

DESCRIPTORES

Heridas y Lesiones; Nanopartículas; Cicatrización de Heridas; Atención de Enfermería; Revisión.

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