INPLASY PROTOCOL

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None declared.

Wound healing therapeutic effect of chitosan nanofibers: a systematic review and meta- analysis of animal studies

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Review question / Objective: **Review question: Does chitosan base nanofibers has significant wound healing therapeutics effects in animal models? A preclinical systematic review of intervention will be carried out to evaluate the therapeutic effects of chitosan nanofibers on animal skin lesions. The PICO (Population, Intervention, Comparator, Outcome) scheme will be used: Intervention: full-thickness skin lesions, and the application of chitosan nanofibers as treatment for animal skin lesions. Regardless of the concentration of chitosan or other added compounds used. Comparison: No intervention, topical placebo agents and standard skin lesions treatments will be included. Outcome: wound healing area, wound closure, type of wound closure (first, second or third intention), healing time, infectious processes (antibacterial/ antifungal properties), blood loss (hemostatic properties) and adverse effects.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 31 October 2022 and was last updated on 31 October 2022 (registration number INPLASY2022100121).

INTRODUCTION

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Rationale: Acute or chronic skin lesions can show delayed and incomplete wound healing, this can affect skin homeostatic systems triggering an increased infection´s risk and metabolic alterations. Reported treatments focus on wound dressings, which are capable of simultaneously treating infections and increasing ulcer healing through chitosan base nanofibers (NFQS). There is a large number of combination elements used with NFQS components (e.g. antiseptic, antibiotic, metals, natural, growth factors, hemostatic and antioxidant), as well as variation in design studies, animal models and outcomes measures, which results in difficulties to compare them directly. Wound healing effects include: rate of wound closure, tissue repair, inflammation, and histological parameters. In this study we aim to provide a systematic review of all animal studies of wound healing with NFQS and focus on the methodological quality through a risk of bias assessment. We will perform a meta-analysis of all the included studies to resolve if NFQS has significant therapeutics wound healing effects in animal models. Other factors as adverse effects and infections added will also be addressed.

Condition being studied: Acute or chronic skin lesions in animal models are the main condition. Skin wounds can be caused by accidents, surgical procedures, diseases (diabetes mellitus), burns or microbial infections, to name a few. Most can be treated on an outpatient basis, however, in some cases complications (e.g. infections, deformities and bleeding) occur that affect dermal homeostasis and result in delayed or incomplete healing. When there are complications, skin wounds usually require medical assistance and specific treatments. Therefore, they constitute a problem of growing concern for health professionals.

METHODS

Search strategy: PubMed Search strategy
#1 Chitosan [MeSH Terms]
#2 chitosan*[Title/Abstract]
#3 #1 or #2
#4 Nanofibers [MeSH Terms]
#5 nanofibrous*[Title/Abstract]
#6 Co-electrospinning*[Title/Abstract]
#7 electrospun*[Title/Abstract]
#8 nanoelectrospinning*[Title/Abstract]
#9 #4 or #5 or #6 or #7 or #8
#10 Wound Healing [MeSH Terms]
#11 Skin Ulcer [MeSH Terms]
#12 Degloving injuries [MeSH Terms]
#13 (skin next ulcer*) or (foot next ulcer*) or (varicose next ulcer*) or (pressure next ulcer*) or (leg next ulcer*)
#14 chronic next wound*[Title/Abstract]
#15 chronic next ulcer*[Title/Abstract]
#16 chronic next injuries*[Title/Abstract]
#17 chronic next skin ulcer*[Title/Abstract]
#18 #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
#19 randomized controlled trial [pt]
#20 controlled clinical trial [pt]
#21 randomized [tiab]
#22 placebo [tiab]
#23 drug therapy [sh]
#24 randomly [tiab]
#25 trial [tiab]
#26 groups [tiab]
#27 #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26
#28 #3 and #9 and #18 and #27.

Participant or population: All healthy animal moldels with acute or chronic skin lessions (all species and all sexes).

Intervention: Full-thickness wound skin lessions model. Skin lessons can be provoked or natural. The intervention will include only the application of chitosan nanofibers as cutaneous lesions treatment. Regardless of the concentration of chitosan or other added compounds used.

Comparator: Topical placebo agents or standard skin lesions treatments.

Study designs to be included: A comparison of chitosan nanofibers applications versus no intervention, topical placebo agents or standard skin lesions treatments.

Eligibility criteria: Another limitations to be consider are no reviews, not duplicated papers, no full paper included. The languages will be only english and spanish. In a period of publication between 2012 to 2022.

Information sources: Databases: PubMed, EBSCO, Elsevier, Wiley, Medline and Springer.

Main outcome(s): As main outcomes: wound healing area, wound closure, type of wound closure (first, second or third intention) and healing time.

Additional outcome(s): Added infectious processes (antibacterial/antifungal properties), blood loss (hemostatic properties) and adverse effects.

Data management: Two of the authors (A, M-C and B, M-C) will perform the data extraction independently, the full information will be collected in the data collection format of the Systematic Review Facility (SyRF) software. The extraction information will be provide from the full text format. figures and tables. If a necessary information is missing the authors will be contacted by e-mail (1 attempt). The extraction from graphs, will be by using a digital image analysis software (ImageJ; http://rsbweb.nih.gov/ij/) by two independent reviewers. If discrepancies are presented, will be resolved by a third part author(D, S-M).

Quality assessment / Risk of bias analysis: Assessment tools specific for pre- clinical animal studies include SYRCLE's risk of bias tool and the CAMARADES checklist for study quality. The presence of biases in the publication results will be critical visual inspection assessed using a Begg's funnel plot and also statistically with the Egger regression test.

Strategy of data synthesis: First a descriptive analysis of the therapeutic effects of the application of NFQS in skin wounds in animal models will be performed, according to the primary and secondary outcomes. Then the type of wounds, the frequency of application of NFQS, the reported therapeutic effects and the characteristics of the intervention will be categorized. A meta analisis of the time and area in the evaluated wound healing process will be performed between NFQS intervention and control groups. A sensivity analisis and a subgroup analysis by characteristics of the intervention (NFQS, dosis) will be perfomed for all outcome selected measures. To identify the heterogeneity of the studies, I^2 statistics and Chi squared test will be performed together (significance level of p-value 0.05).

Subgroup analysis: The subgroups will be analyzed according to the NFCS dose and added compounds.

Sensitivity analysis: A sensitivity analysis will be developed in order to test the impact of decision making during the sistematic review, this will include an analysis of the study quality, also, ordinal scales analisis along with the modelling with an alternative method (random-effects).

Language restriction: English and spanish.

Country(ies) involved: México.

Other relevant information: This is an update of our earlier systematic review: Maldonado-Cabrera, B., Sánchez-Machado, D. I., López- Cervantes, J., Osuna-Chávez, R. F., Escárcega-Galaz, A. A., Robles-Zepeda, R. E., & Sanches-Silva, A. (2021). Therapeutic effects of chitosan in veterinary dermatology: a systematic review of the literature. Preventive Veterinary Medicine, 190, 105325. https://doi.org/10.1016/j.prevetmed.2021.105325

Keywords: Animal, Chitosan nanofiber, Clinical trial, Full-thickness skin lession, Wound healing.

Dissemination plans: In addition to producing a report for the funders of this review, a paper will be submitted to a leading journal in this field.

Contributions of each author:

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