INPLASY

The Role of Cold Atmospheric Plasma Therapy in Chronic Wound Healing: A Systematic Review and Meta-analysis

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ADMINISTRATIVE INFORMATION

Support - No.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202510096

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 January 2025 and was last updated on 23 January 2025.

INTRODUCTION

Review question / Objective To evaluate the efficacy of cold atmospheric plasma (CAP) therapy in improving chronic wound healing outcomes
To assess secondary outcomes such as pain reduction, infection control, and patient satisfaction.
To determine the safety and tolerability of CAP therapy.

Rationale Does CAP therapy accelerate wound healing compared to standard care or placebo?
What is the impact of CAP therapy on pain, infection rates, and scar quality?
Are there any safety concerns associated with CAP therapy?

Condition being studied Chronic Wounds – including diabetic foot ulcers, venous leg ulcers, and pressure ulcers. These wounds are characterized by delayed healing due to impaired tissue regeneration, prolonged inflammation, and increased risk of infection. Chronic wounds are a major healthcare burden, leading to reduced quality of life and significant healthcare costs.
Cold Atmospheric Plasma (CAP) therapy is being investigated as a novel, non-invasive treatment that can potentially accelerate wound healing, reduce microbial load, and improve tissue regeneration in patients with chronic wounds. This systematic review aims to synthesize existing evidence from randomized controlled trials to evaluate the efficacy and safety of CAP therapy compared to standard wound care treatments.

METHODS

Search strategy Search Terms (Keywords and Boolean Operators)
The following comprehensive search terms will be used to identify relevant studies across multiple databases:

1. Population (Chronic Wounds):

"Chronic Wound" OR "Non-Healing Wound" OR "Diabetic Foot Ulcer" OR "Venous Leg Ulcer" OR "Pressure Ulcer" OR "Hard-to-Heal Wound"
2. Intervention (Cold Atmospheric Plasma Therapy):

"Cold Atmospheric Plasma" OR "CAP Therapy" OR "Plasma Medicine" OR "Non-Thermal Plasma" OR "Low-Temperature Plasma"
3. Comparator (Standard Wound Care):

"Conventional Wound Treatment" OR "Standard Wound Dressing" OR "Moist Wound Healing" OR "Wound Care Protocol"
4. Outcomes (Wound Healing and Associated Measures):

"Wound Healing Rate" OR "Tissue Regeneration" OR "Granulation Tissue Formation" OR "Wound Closure" OR "Reduction in Wound Size" OR "Infection Control"
5. Study Type:

"Randomized Controlled Trial" OR "RCT" OR "Clinical Trial" OR "Controlled Clinical Trial"
Electronic Databases to Be Included in the Review
The following electronic databases will be searched to ensure comprehensive coverage of relevant studies:

PubMed/Medline

Search Strategy:
("Cold Atmospheric Plasma" OR "CAP Therapy" OR "Plasma Medicine")
AND ("Chronic Wound" OR "Diabetic Foot Ulcer" OR "Pressure Ulcer" OR "Venous Leg Ulcer")
AND ("Randomized Controlled Trial" OR "RCT" OR "Clinical Trial")

Cochrane Central Register of Controlled Trials (CENTRAL)

"Cold Atmospheric Plasma" OR "Plasma Therapy"
AND "Chronic Wound" OR "Diabetic Foot Ulcer"
AND "Randomized Controlled Trial"

Scopus

TITLE-ABS-KEY ("Cold Atmospheric Plasma" OR "CAP Therapy" OR "Plasma Medicine")
AND TITLE-ABS-KEY ("Chronic Wound" OR "Diabetic Foot Ulcer")
AND TITLE-ABS-KEY ("Randomized Controlled Trial")

ClinicalTrials.gov

"Cold Atmospheric Plasma" AND "Chronic Wound" AND "RCT"

Filters Applied:

Study Type: Interventional (Clinical Trial)
Status: Recruiting, Active, Completed
Results: Studies With Results
Study Start Date: From 2005 to Present

Google Scholar (For Gray Literature and Preprints)
"Cold Atmospheric Plasma" OR "CAP Therapy" OR "Plasma Medicine" AND "Chronic Wound" OR "Diabetic Foot Ulcer" OR "Pressure Ulcer" OR "Venous Leg Ulcer" OR "Non-Healing Wound" AND "Randomized Controlled Trial" OR "RCT" OR "Clinical Trial" AND "Wound Healing" OR "Tissue Repair" OR "Granulation Tissue" "Cold Atmospheric Plasma" AND "Chronic Wound" AND "RCT"

Search Filters to Be Applied Across All Databases
Language: English
Publication Date: From 2005 to present
Study Type: Randomized Controlled Trials (RCTs)
Population: Human studies only.

Participant or population This systematic review focuses on patients with chronic wounds, including but not limited to the following types:

Diabetic Foot Ulcers (DFUs):

Patients diagnosed with diabetes mellitus experiencing chronic, non-healing foot ulcers.
Ulcers classified according to standard grading systems (e.g., Wagner, University of Texas classification).
Venous Leg Ulcers (VLUs):

Patients with chronic venous insufficiency leading to persistent lower limb ulcers.
Diagnosed through clinical assessment and Doppler studies.
Pressure Ulcers (PUs):

Individuals at risk due to immobility, pressure, or friction-related wounds, commonly found in bedridden or elderly patients.
Classified based on severity (e.g., Stage I-IV by NPUAP/EPUAP).
Inclusion Criteria:

Adults (≥18 years) diagnosed with chronic wounds lasting more than 4 weeks.
Patients receiving cold atmospheric plasma (CAP) therapy as an intervention.

Studies focusing on RCTs with clearly defined outcomes related to wound healing.
Exclusion Criteria:

Pediatric patients (<18 years).
Patients with malignant wounds or wounds due to infectious diseases.
Animal studies or in-vitro research.
Setting:
The population includes individuals treated in hospital outpatient clinics, wound care centers, and community-based healthcare settings.

Intervention The intervention being examined in this systematic review is Cold Atmospheric Plasma (CAP) Therapy, a novel, non-thermal treatment approach for chronic wound healing. CAP therapy involves the application of ionized gas containing reactive oxygen and nitrogen species to the wound site, promoting healing through antimicrobial activity, anti-inflammatory effects, and stimulation of tissue regeneration. Various CAP devices have been utilized in clinical studies, including handheld plasma devices, dielectric barrier discharge (DBD) plasma, plasma jets, and atmospheric pressure plasma systems. The therapy is typically applied directly to the wound surface, with treatment frequency ranging from daily to weekly sessions, and session durations varying from a few minutes to longer exposures depending on the protocol used in the trials. CAP therapy has been shown to exert a bactericidal effect against multidrug-resistant microorganisms, stimulate angiogenesis, and enhance fibroblast proliferation, all of which contribute to improved wound healing outcomes. In the included randomized controlled trials, CAP therapy is often compared to standard wound care interventions, such as wound dressings, saline irrigation, debridement, and other conventional treatment modalities. Some studies also include placebo groups where patients receive inactive plasma exposure or sham therapy to assess the true efficacy of CAP treatment. This systematic review aims to evaluate the effectiveness and safety of CAP therapy in chronic wound management compared to these established treatment options.

Comparator The comparator interventions in this systematic review include standard wound care treatments and placebo or sham interventions commonly used in clinical practice for managing chronic wounds. Standard wound care typically consists of conventional approaches such as wound dressings (e.g., hydrocolloid, alginate, or foam dressings), saline irrigation, debridement, and antimicrobial therapy. These conventional methods aim to promote wound healing by maintaining a moist environment, preventing infection, and facilitating tissue regeneration. In addition to standard care, some studies include comparators such as advanced wound therapies, including negative pressure wound therapy (NPWT) and advanced dressing technologies, to assess the relative effectiveness of Cold Atmospheric Plasma (CAP) therapy. Furthermore, placebo or sham treatments, which may include the application of inactive plasma devices or exposure to air without plasma activation, are used in some trials to provide a control measure for assessing the specific effects of CAP therapy. The comparators will allow for an objective evaluation of CAP therapy's efficacy in terms of wound healing rate, infection control, pain reduction, and overall treatment outcomes in chronic wound management.

Study designs to be included This systematic review will include randomized controlled trials (RCTs) that evaluate the efficacy and safety of Cold Atmospheric Plasma (CAP) therapy in chronic wound healing. RCTs are considered the gold standard for clinical research and provide the highest level of evidence by minimizing bias and allowing for direct comparisons between intervention and control groups.

Eligibility criteria This systematic review will include studies that meet specific eligibility criteria to ensure the synthesis of high-quality evidence. Eligible studies will include adult patients (≥18 years) diagnosed with chronic wounds, such as diabetic foot ulcers, venous leg ulcers, pressure ulcers, and non-healing surgical wounds. The intervention of interest is Cold Atmospheric Plasma (CAP) therapy, either as a standalone treatment or in combination with standard wound care. Comparators may include standard wound care interventions, placebo, sham therapy, or other advanced wound healing treatments. Studies must report at least one relevant clinical outcome, including wound healing rate, pain reduction, infection control, quality of life improvement, or the safety and adverse effects of CAP therapy. Only randomized controlled trials (RCTs) with clearly defined intervention and comparator groups will be considered for inclusion. The review will focus on studies published in English from 2005 to the present to ensure relevance to current clinical practice. Studies will be excluded if they are non-randomized, observational studies, case reports, conference abstracts, reviews, animal studies, or in vitro experiments. Additionally, studies involving patients with malignant wounds, burns, or acute wounds, as well as those with insufficient data on CAP therapy or unclear outcome reporting, will not

be included. Duplicates and studies with overlapping patient populations will also be excluded to maintain data integrity.

Information sources The information for this systematic review will be sourced from a comprehensive search of electronic databases, clinical trial registries, and grey literature to ensure a thorough and unbiased collection of relevant studies. The primary databases to be searched include PubMed, PubMed Central, Cochrane Central Register of Controlled Trials (CENTRAL), and Scopus, which provide access to peer-reviewed literature and high-quality randomized controlled trials (RCTs). Additionally, ongoing and completed trials will be identified through searches in ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), and the EU Clinical Trials Register to capture any unpublished or ongoing research. Grey literature, including conference proceedings, white papers, and preprints, will be retrieved from sources such as Google Scholar ensuring inclusion of relevant but unpublished studies. A manual search of reference lists from relevant systematic reviews and meta-analyses will also be conducted to identify additional studies. Closed-access articles will not be included in the review to ensure accessibility and reproducibility of findings. No restrictions will be placed on the publication status, and efforts will be made to include the most up-to-date evidence in the field. Studies published in English from 2005 to the present will be considered for inclusion. All search strategies will be designed to maximize sensitivity and specificity, with a focus on identifying relevant literature that aligns with the study's inclusion criteria.

Main outcome(s) The primary outcome of this systematic review is the wound healing rate, which will be assessed through parameters such as the percentage of wound closure, reduction in wound size, and time to complete epithelialization. These outcomes will provide a quantitative measure of the efficacy of Cold Atmospheric Plasma (CAP) therapy in promoting tissue regeneration and wound closure. Secondary outcomes will include pain reduction, measured using validated pain scales such as the Visual Analog Scale (VAS), and infection control, assessed through microbiological analysis or clinical signs of infection resolution. Additionally, the review will evaluate quality of life improvements, as reported by patients using standardized quality-of-life assessment tools, and the safety and tolerability of CAP therapy, measured by the incidence of adverse events such as skin irritation, discomfort, or delayed healing. The synthesis of these outcomes will provide comprehensive insights into the clinical effectiveness and safety profile of CAP therapy in the management of chronic wounds.

Additional outcome(s) In addition to the primary outcomes, this systematic review will assess several additional outcomes to provide a comprehensive evaluation of Cold Atmospheric Plasma (CAP) therapy in chronic wound management. These outcomes include duration of hospitalization, which reflects the impact of CAP therapy on healthcare resource utilization and overall patient recovery. Recurrence rates of chronic wounds after initial healing will also be analyzed to determine the long-term effectiveness of CAP therapy compared to standard wound care. Furthermore, the review will evaluate patient satisfaction and adherence to treatment, as measured by self-reported questionnaires and adherence rates to prescribed treatment regimens. The impact of CAP therapy on inflammatory markers, such as C-reactive protein (CRP) and pro-inflammatory cytokines, will also be considered to understand the potential mechanistic effects of the treatment. Lastly, the review will explore economic outcomes, including cost-effectiveness analyses where available, to assess the financial implications of implementing CAP therapy in clinical practice.

Data management All data collected during this systematic review will be managed using Covidence, a cloud-based platform designed to facilitate the systematic review process by ensuring consistency, transparency, and accuracy. Covidence will be used for study screening, data extraction, and quality assessment, allowing for efficient collaboration between the two authors. The platform enables blinded screening, tracking of decisions, and conflict resolution between the authors. A standardized data extraction form will be utilized to capture essential study details, including study characteristics, participant demographics, intervention specifics, outcome measures, and risk of bias assessments. Extracted data will be securely stored within Covidence, with regular backups to prevent data loss. A PRISMA-compliant flow diagram will be generated within Covidence to document the study selection process, including the number of records identified, screened, included, and excluded, along with reasons for exclusions. Any discrepancies during data extraction will be resolved through mutual discussion between the two authors. Finalized data will be archived and made available as supplementary materials upon publication to ensure transparency and facilitate future research efforts.

Quality assessment / Risk of bias analysis The quality assessment and risk of bias analysis for the included studies will be conducted using the Cochrane Risk of Bias (RoB 2.0) tool, which is specifically designed for evaluating randomized controlled trials (RCTs). This tool assesses bias across five key domains: (1) bias arising from the randomization process, (2) bias due to deviations from the intended interventions, (3) bias due to missing outcome data, (4) bias in the measurement of the outcome, and (5) bias in the selection of the reported results. Each domain will be assessed and categorized as having a low, high, or some concern for risk of bias. The two authors will independently evaluate the included studies, and discrepancies will be resolved through discussion to reach consensus.

Additionally, the overall quality of the evidence will be assessed using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach. The GRADE framework evaluates the certainty of evidence based on criteria such as study limitations, consistency of results, indirectness, imprecision, and publication bias. The evidence will be classified into four levels: high, moderate, low, or very low certainty.

To ensure transparency, risk of bias summaries and justifications will be presented in tables and narrative format. Any potential sources of bias identified during the assessment will be reported and considered in the interpretation of the review findings.

Strategy of data synthesis The strategy for data synthesis in this systematic review will focus on rigorously combining and analyzing data extracted from eligible randomized controlled trials (RCTs) evaluating the efficacy of cold atmospheric plasma (CAP) therapy in chronic wound healing. Data extraction will be conducted independently by two reviewers using a standardized form within the Covidence platform, capturing key study characteristics (author, year, design, sample size), participant demographics (age, wound type, duration), intervention details (CAP device, treatment parameters, frequency, duration), comparator details (standard care, placebo), and outcome data (wound healing rate, pain scores, infection rates, adverse events). Discrepancies in extracted data will be resolved through discussion or consultation. Heterogeneity between studies will be statistically assessed using the I^2 statistic, with values of 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively. If sufficient data are available, a meta-analysis will be performed to pool the results of included studies using a random-effects model to account for potential variations between studies.

Subgroup analysis Subgroup analyses will be conducted to explore potential differences in treatment effects based on wound type (diabetic foot ulcer, venous leg ulcer, pressure ulcer) and CAP device type.

Sensitivity analysis Sensitivity analyses will be performed by excluding studies with high risk of bias, as determined by the Cochrane Risk of Bias 2.0 tool, to assess the robustness of the overall findings. If meta-analysis is not appropriate due to substantial heterogeneity or insufficient data, a narrative synthesis will be conducted. This will involve a descriptive summary of the findings from the included studies, focusing on the direction and consistency of effects across studies. Finally, publication bias will be assessed using funnel plots and Egger's test if at least 10 studies are included in the meta-analysis to evaluate the potential for selective reporting of positive results.

Language restriction The systematic review will include only studies published in the English language. This restriction is implemented due to resource constraints and the expertise of the review team, which is proficient only in English. While this may potentially exclude relevant research published in other languages, it is a pragmatic decision to ensure the review's feasibility and accurate interpretation of included studies. The potential impact of this language restriction on the review's findings will be acknowledged as a limitation.

Country(ies) involved Malaysia, US.

Keywords Cold Atmospheric Plasma; CAP Therapy; Plasma Medicine; Non-Thermal Plasma; Low-Temperature Plasma; Plasma Treatment; Chronic Wound; Non-Healing Wound; Wound Healing; Wound Management; Diabetic Foot Ulcer; Venous Leg Ulcer; Pressure Ulcer; Decubitus Ulcer; Ischemic Ulcer; Leg Ulcer; Skin Ulcer; Tissue Regeneration; Granulation Tissue Formation; Wound Closure; Wound Size Reduction; Infection Control; Antimicrobial Therapy; Pain Management; Pain Reduction; Scarring; Scar Quality; Adverse Events; Safety; Efficacy; Randomized Controlled Trial; RCT; Clinical Trial; Atmospheric Pressure Plasma; Plasma Jet; Dielectric Barrier Discharge; DBD; Standard Wound Care; Conventional Wound Treatment; Moist Wound Healing.

Dissemination plans The primary dissemination plan is to submit the findings of this systematic review to a peer-reviewed journal such as Wound Repair and Regeneration, JAMA Dermatology, or The British Journal of Dermatology."Efforts will be made to publish the review in an open-access format to ensure broad accessibility.The findings will also be considered for presentation at relevant conferences, such as the European Wound Management Association (EWMA) conference or the Wound Healing Society (WHS) meeting.

Contributions of each author

Author 1 - Mudassar Arain - Author 1 will edit and review the manuscript and be involved in the screening process.
Email: arainm@uncw.edu
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