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# Effectiveness of topical treatment for pain control of malignant fungating wound in adults compared to systemic treatment: a systematic review protocol

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# Effectiveness of topical treatment for pain control of malignant fungating wound in adults compared to systemic treatment: a systematic review protocol.


## Abstract

Objective: To synthesize the evidence of the effectiveness of topical treatment compared to the systemic treatment for pain control in Malignant Fungating Wounds (MFWs) in adults.

Introduction: Approximately 14.5% of cancer patients present MFWs due to the increased survival rate of oncology treatments, and 85% report pain in the wound. Previous systematic reviews on the subject have explored MFWs-related symptoms (bleeding, foul odor, and exudate) but without results concerning the pain. A recently published scoping review mapped 20 proposals for topical treatment of MFWs-related pain, originated in different studies designs. Currently, there is a need to carry out an effectiveness review in order to facilitate clinical evidence-based decision-making.

Inclusion criteria: Quantitative studies on the effects of topical therapies for pain control in MFWs compared to systemic treatments in adult patients in English, Portuguese, and Spanish without any time limits. Studies that do not meet 70% of the methodological quality threshold will be excluded.

Methods: A review of effectiveness according to the JBI methodology. The titles and abstracts of identified records will be checked for the inclusion criteria, and the selected papers will be reviewed in their entirety for their relevance to the objective. The selection of the studies will be carried out according to the defined threshold of the assessment of the methodological quality using the JBI Critical Appraisal Checklist instruments, and the data of interest will be extracted by two reviewers. Finally, the data synthesis will be presented in a narrative and/or statistical summary.

Systematic review registration number: CRD42022351715


**Keywords:** Malignant fungating wound, nursing, pain, systematic review, topical therapy.

## Introduction

In 2020, 19.3 million people were diagnosed with cancer worldwide, and the global burden of cancer is expected to reach 28.4 million cases by the year 2040.[1] The current cancer situation becomes more and more relevant as new diagnostic and therapeutic technologies are developed, thus improving patient survival and transforming the inexorable determinism of cancer as a lethal disease.[2]

The increased survival rate of patients with advanced cancer brings with it certain challenges, such as the development of tumor-related wounds called Malignant Fungating wounds (MFWs).[3] These are chronic and more frequently irreversible injuries caused by the uncontrolled proliferation of malignant fungating cells that infiltrate by local invasion and damage the structures of the skin, subcutaneous and muscular tissues, and even affect bones.[4] Through the process of oncogenesis[5] a progressive and degenerative evolution of MFWs occurs, which is caused by primary neoplasia and metastasis.[4] The general incidence of MFWs ranges from 5%[4] to 14.5%[6], and due to cutaneous metastases, it can range from 0.6% to 10.4%.[7]

MFWs occur particularly in patients with breast cancer with a prevalence of 49%, followed by localization in the head and neck with 21%, 17% in the extremities and genitals, and 13% in the head.[8] Concerning skin affectations, symptoms of bleeding, pain, exudation, and foul odor,[6,9] are the main consequences of MFWs and can lead to the development of complications such as superficial and/or systemic infections, fistulas, and larval infestation. These wounds constitute another aggravation in the cancer patient's life as they progressively disfigure the body.[6] Therefore, the management of symptoms can have repercussions in reducing emotional anguish for patients, favoring their quality of life, and affecting the control of public health expenses since it can result in hospitalizations and treatments that could be avoided.[9]

Patients with MFWs receive topical treatments that may include: antimicrobial properties (silver dressings, manuka honey); [10] substances with analgesic effects, such as opioids (topical morphine);[10-11] anti-inflammatories (topical ibuprofen);[10] anesthetics (lidocaine gel and topical benzocaine);[12] lidocaine and prilocaine (Eutectic Mixture of Local Anesthetics, EMLA);[10] for the control of bleeding topical treatments consisted of hemostatic coatings (calcium alginate, surgical hemostats: gel foam, regenerated oxidized cellulose, thrombin), non-adherent coatings (trilaminate hydro cellular dressing, 100% polyester, silicone), vasoactive drug (adrenaline) and sclerosing substances,[13] these results suggest that the cited

interventions should be considered with caution in clinical practice due to the low level of evidence;[13] for odor control (topical metronidazole, polyhexamide biguanide,[10] activated carbon dressing, curcumin ointment and green tea extract) as an essential traditional phytotherapy has antimicrobial effect and also suppresses malodor,[14] there is also weak evidence to suggest that foam dressings containing silver may be effective in reducing bad smell.[15]

Pain in MFWs is present in 85% of patients with advanced cancer.[16] The exact mechanism that triggers physical pain in MFWs can be related to several causes, be it isolated or combined, such as accelerated tumor growth with pressure and invasion of the structures and nerve endings of the skin which can be nociceptive and neuropathic;[17] infections with a concentration of more than $10^5$/g of bacteria;[18] edema;[19] excess of exudate (dermatitis associated with humidity)[20] and dressing changes.[20]

The type of pain experienced by the person with MFWs depends on the location of the wound, degree of tissue damage, nerve involvement, and the patient's previous experience with analgesics. Each of these factors creates a different type of pain, intensity, duration, and sensation.[21]

The clinical practice of topical interventions for controlling pain as a symptom in MFWs requires using dressings based on scientific evidence, the ability to use cutting-edge treatments, and access to advanced therapies.[5]

A preliminary search was carried out for systematic reviews of the effectiveness of topical therapeutics for pain control in MFWs using the “malignant fungating wounds” AND “pain” equation in the following databases: JBI, Cochrane, Epistemonikos, ACCESS, DARE, MEDLINE, and PROSPERO without a language or date restriction. Among the findings, only a systematic review of effectiveness from 2017 was recovered, being non-specific for the pain symptom.[22] this review aimed to assess the efficacy of topical treatment of infection, odor, and pain in MFWs. Articles published between 2008 and 2017 were included. Due to the inclusion criteria, no studies for pain control in MFWs were considered, and insufficient evidence was identified in the included studies.[22]

Another finding was the review registry in the JBI journal in 2019 called "Topical therapy for pain management of malignant fungating wounds: a scoping review protocol" [23], which aimed to map the existing evidence of topical therapies and/or treatments for the management of MFWs-related pain. This review identified studies on the effectiveness of topical treatment for

pain control in malignant fungating wounds. The authors found 20 proposals for topical therapies for pain control in MFWs in articles between 1995 and 2020, which were synthesized into the following categories:

- Dressings: non-adherent, hydrogel, absorbent, and anti-inflammatory.[24]

- Pain reliever drugs: topical opioids, topical anesthetics, and medical cannabis.[25]
- Antimicrobial substances: honey and antiseptics.[26]

The topical therapies applied to the periwound skin synthesized in the review were: zinc oxide (ointment and cream), silicone (adhesive remover), dimethicone, petroleum jelly, acrylate, cyanoacrylate, hydrocolloid (plaque and powder), and vitamin A and D ointment.[23]

After verifying the lack of published systematic reviews, protocols, or registered titles, which focus on the effectiveness of topical therapy for pain control due to MFWs, the need to carry out the present review is concluded.

Likewise, this systematic review will gain significance in evidence-based clinical practices and in the advancement of nursing care for cancer patients with malignant tumor wounds in relation to safety and quality of care; impact on quality of life-related to symptom improvement; and likewise, the quality of life of caregivers. This review aims to synthesize the evidence related to the effectiveness of topical treatment for pain control in malignant fungating wounds in adults compared to systemic treatments.

**Review question**

What is the effectiveness of topical dressing-type therapies, analgesic drugs, and antimicrobial substances for pain control in MFWs in adults over 18 years of age compared to systemic treatment?

**Inclusion criteria**

**Participants**

This review will consider studies that include adults with painful MFWs, without restricting races, ethnicities, and genders. According to the World Health Organization,[27] people over 18 years will be considered adults.

**Intervention**

The systematic review will consider studies that investigate the effectiveness of topical therapeutics for the management of MFWs pain of the dressing type (non-adherent, hydrogel, absorbent, and anti-inflammatory), antimicrobial substances (honey and antiseptics), and analgesic substances (topical opioids, anesthetics topics).[23] All studies where the effect of any topical treatment (substance) applied to MFWs is described will be included. In addition, the following aspects will be considered: substance, frequency, dose, presentations, intensity, and roles of the multidisciplinary team.

**Comparator**

The comparator will be the systemic treatment for pain control in MFWs in adults over 18. The following aspects will be considered: substance, frequency, dose, presentations, intensity, and roles of the multidisciplinary team.

**Outcomes**

The systematic review will consider studies that include pain improvement as a primary outcome (assessed during topical and systemic therapy, using pain assessment scales, questionnaires, and other validated tools) and adverse events as a secondary outcome, these being the harm caused to the patient from health care or intervention and that is not produced intentionally,[28] health-related quality of life and costs. Additionally, the available standardized sets of results for the relevant tests will be checked for the present review of the international COMET initiative (Core Outcome Measures in Effectiveness Trials).

**Types of studies**

This review will consider experimental study designs. In the absence of randomized controlled trials, other designs will be considered, including quasi-experimental studies, randomized controlled trials, non-randomized controlled trials, before and after studies, and series studies. In addition, observational analytical studies, including prospective and retrospective cohort studies, will be considered for inclusion. Studies published in English, Portuguese, and Spanish will be included without time limits.

**Methods**

The proposed systematic review will be carried out following the methodology for systematic effectiveness reviews proposed by JBI[29] and is registered on the PROSPERO CRD42022351715 platform.

**Search strategy**

The search strategy aims to locate published and unpublished studies. An initial limited search of MEDLINE and CINAHL was carried out to identify articles on the topic. The text words contained in the titles and abstracts of the relevant articles, and the index terms used to describe the articles, were used to develop a comprehensive search strategy for CINAHL (see Appendix I). The search strategy, including all identified keywords and index terms, will be tailored for each source of information. The search will not be limited to the year of publication. The reference list of all studies for critical evaluation will be selected for further analysis.

The databases that will be used are CINAHL, LILACS, Embase, Scopus, Web of Science, PubMed, Cochrane, NICE, Scopus, and JBIEBP. Likewise, unpublished quantitative studies will be sought after in CAPES Thesis Bank (Brazil), Google Scholar (including textbooks and conference proceedings), Teseo (Doctoral Thesis Database - Spain), RCAAP (Open Access Scientific Deposit - Canada), Canadian Thesis, and Thesis Portal and Dart -E (European Database of Theses and Dissertations) and in the international initiative called All Trials and Restoring invisible and Abandoned Trials.

**Study selection**

After the search, all identified records will be pooled and registered with Mendeley (Mendeley Ltd. 2020, Elsevier, The Netherlands), and duplicate studies will be removed. Two independent reviewers will then screen the titles and abstracts to assess them against the inclusion criteria specified previously in the review protocol. Potentially relevant studies will be retrieved in their entirety, and citation data will be imported into the JBI System for Unified Management, Evaluation, and Review of Information (JBI SUMARI 2017; JBI, Adelaide, Australia). Two independent reviewers will evaluate the full text of the selected citations in detail against the inclusion criteria. Reasons for excluding full-text studies that do not meet the inclusion criteria will be recorded and reported in the systematic review. Any disagreement between the reviewers at any stage of the study selection process will be resolved through discussion or with a third reviewer. The results of the study search and inclusion process will be reported in full in the final systematic review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow chart.[30]

**Assessment of methodological quality**

Eligible studies will be critically evaluated by two independent reviewers using JBI critical evaluation instruments,[31] with answer options “Yes,” “No,” “Unclear,” and “Not Applicable” for the following types of studies: randomized controlled trials; quasi-experimental studies; and cohort studies. Any disagreement between the reviewers will be resolved by further discussion

with a third critical reviewer. The results of the critical evaluation will be reported in narrative and table form. After the critical evaluation, studies that do not meet 70% of the quality threshold will be excluded. This decision will be based on:

- JBI Critical Appraisal Checklist for Randomized Controlled Trials Instrument: it has 13 evaluation items, and the cutoff score is 9.1.
- JBI Critical Appraisal Checklist for Quasi-Experimental Studies: the instrument has nine evaluation items, and the established cut-off score is 6.3.
- The JBI Critical Appraisal Checklist for Cohort Studies Instrument has 11 assessment items, and the defined cohort score is 7.7.

**Data extraction**

Two independent reviewers will extract data of interest using the modified standardized data extraction tool[29] (Appendix II), and a credibility level will be assigned. The extracted data will include specific details about populations, study methods, interventions, and results of relevance to the purpose of the review indicating specific details. Any reviewer disagreement will be resolved through discussion or with a third reviewer. When necessary, the authors of the articles will be contacted to request missing or additional data via e-mail.

**Data synthesis**

Where possible, studies will be pooled in a statistical meta-analysis using JBI SUMARI. Effect sizes will be expressed as weighted (or standardized) odds ratios (for dichotomous data) and weighted (or standardized) post-intervention final mean differences (for continuous data), and their 95% confidence intervals will be calculated for analysis. Heterogeneity will be assessed statistically using the I2 and standard $\chi 2$ tests. The choice of the model (random or fixed effects) and the method for the meta-analysis will be based on the guidance of Tufanaru et al.[32] Experimental and observational data will be synthesized in separate meta-analyses for each outcome. The impact of study quality and differences in sample size, age of patients (adult versus older adult), and insertion technique (blunt dissection versus Seldinger) will be explored using a sensitivity analysis.

When statistical grouping is not possible, results will be presented in a narrative form, including tables and figures to aid in data presentation when appropriate. A funnel plot will be generated to assess publication bias if ten or more studies are included in a meta-analysis. Statistical tests for funnel plot skewness (Egger's test, Begg's test, Harbord's test) will be performed where appropriate.

## Assessing certainty in the findings

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach[33] will be taken to rate the certainty of the evidence, and a Summary of Findings (SoF) will be created using the GRADEpro software (2020, McMaster University, ON, Canada). The SoF will present the following information where appropriate: absolute risks for treatment and control, estimates of relative risk, and a rating of the quality of the evidence based on the risk of bias, openness, heterogeneity, precision, and risk of publication bias of the review results.

The outcomes reported in the SoF will be pain control of dressings, analgesic drugs, antimicrobial substances, and standard treatment in malignant fungating wounds.

**Authors Contribution:**
Yesly Johana Rincón Torres: Conceptualization, Writing-review, editing
Suzana Aparecida da Costa Ferreira: Conceptualization, Writing-review, editing
Carol Viviana Serna González: Conceptualization, Writing-review, editing
Sandra Guerrero Gamboa: Conceptualization, Writing-review, editing
Vilanice Alves de Araujo Püschel: Conceptualization, Writing-review, editing
Vera Lúcia Conceição de Gouveia Santos: Conceptualization, Writing-review, editing

**Conflicts of interest:** There are no conflicts of interest.

**Data availability statement:** Does not apply to this article as no new data was created or analyzed in this study

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