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TOPICAL MORPHINE FOR PATIENTS WITH PAINFUL NEOPLASTIC WOUNDS: A RANDOMIZED CLINICAL TRIAL PROTOCOL

MORFINA TÓPICA PARA PACIENTES COM FERIDAS NEOPLÁSICAS DOLOROSAS: PROTOCOLO DE ENSAIO CLÍNICO RANDOMIZADO

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RESUMO

Objetivo: Analisar a efetividade da morfina tópica no controle da dor local e na promoção do conforto em pacientes com feridas neoplásicas em mama, cabeça ou pescoço. **Método:** Ensaio clínico randomizado de fase II, duplo-cego, realizado em centro único. O estudo pretende incluir 106 pacientes com feridas neoplásicas malignas nessas regiões, maiores de 18 anos, com escore mínimo de três na escala numérica de avaliação da dor (0-10). **Resultados esperados**: Os principais desfechos avaliados serão a intensidade média da dor, alívio médio da dor, escore de conforto, dosagem de morfina sistêmica e incidência/classificação de eventos adversos. **Registro:** ClinicalTrials.gov (NCT05800834).

Descritores: Dor; Ferimentos e Lesões; Morfina; Mama; Neoplasias de Cabeça e Pescoço; Cuidados Paliativos.

ABSTRACT

Objective: To analyze the effectiveness of topical morphine in controlling local pain and promoting comfort in patients with neoplastic wounds in the breast, head, or neck. **Method:** A randomized, double-blind, phase II clinical trial conducted in a single center. The study aims to include 106 patients with malignant neoplastic wounds in these regions, over 18 years of age, with a minimum score of three on the numerical pain assessment scale (0-10). **Expected results:** The main outcomes evaluated will be average pain intensity, average pain relief, comfort score, systemic morphine dosage, and incidence/classification of adverse events. **Registration:** ClinicalTrials.gov (NCT05800834).

Descriptors: Pain; Wounds and Injuries; Morphine; Breast; Head and Neck Neoplasms; Palliative Care.

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INTRODUCTION

Overall, 55–95% of patients with neoplastic wounds experience local pain[1]. Pain in neoplastic wounds is a complex pathophysiological process, as cancer cells compress wound bed tissue, peripheral blood vessels, and nerves, resulting in severe pain[2].

In order to reduce local pain, measures such as delicate removal of the dressing, administration of analgesic medication before manipulation and use of 2% lidocaine gel as primary dressing can reduce the painful sensation[3].

A series of case studies evaluated topical morphine gel for local pain reduction in patients with epidermolysis bullosa (EB), a rare genetic disorder characterized by chronic painful wounds. Topical morphine gel was used as adjunctive therapy in three patients with EB. The case studies suggest a positive effect of topical morphine gel on painful wounds across a spectrum of EB subtypes.

In this study, the gel used had a morphine concentration of 0.1% w/v in Intrasite Gel (morphine 10 mg in 10 ml of a premixed hydrogel, packaged in a 10 ml Luer-lok syringe). The three cases (recessive dystrophic EB, inverse recessive dystrophic EB and junctional EB) suggested a positive effect of topical morphine gel on painful wounds in different EB subtypes.

The results suggest that, in addition to routine wound care, topical morphine gel may be an adjuvant and, in some cases, an alternative to systemic analgesia, especially when this includes poorly tolerated strong opioids[4].

The use of topical morphine gel was evaluated in a study of adult hospitalized patients with chronic wounds. Systemic opioid use and pain intensity were characterized before and after initiation of morphine gel, using morphine equivalent daily dose and Pain Rating Scale scores as measures.

Twenty-three patients received 371 applications of topical morphine gel. The mean number of applications received was 8.0 [5.0 to 26.0] per patient. The mean change in daily morphine equivalent dose 24 hours after starting morphine gel was 0.0 mg [-15.3 to 11.3] (n=21); 48 hours later it was -4.4 mg [-27.5 to 8.8] (n=20); and 1 week later it was -7.5 mg [-41.9 to -0.3] (n=12).

The median change in pain score 24 hours after starting morphine gel was 0.0 [-0.5 to 1.5] (n=13); 48 hours later, it was -0.5 [-3.25 to 0.0] (n=14); and 1 week later, it was 1.0 [-1.0 to 3.5] (n=9). In this analysis, patients treated with morphine gel required lower doses of systemic opioids, suggesting that topical morphine gel may provide analgesia while reducing the need for systemic opioids[5].

A Dutch study developed a sterile morphine hydrogel for the treatment of painful wounds. Poloxamer 407 hydrogel with a concentration of 5 mg/g (0.5% w/w) morphine hydrochloride, packaged in a plastic syringe system, was used.

Sterility tests showed that the product was sterile both immediately after production and sterilization and after 20 months of storage. The stability of morphine hydrochloride was assessed by monthly concentration analysis. Morphine hydrochloride concentrations remained between 90% and 110% of the theoretical concentration for a period of 36 months when stored at room temperature and protected from light, suggesting excellent stability and safety regarding the use of the gel[6].

A study conducted in Kenya developed a topical ointment containing fixed amounts of morphine and lidocaine specifically for use on malignant wounds. Ninety milligrams of 2% lidocaine gel was mixed with 80 mg of oral morphine sulfate (tablets) and crushed in a container until the mixture was consistent and homogeneous.

Four to eight milliliters of the gel, depending on the size of the wound, were applied to a gauze pad and placed over the wound every eight hours. The five patients evaluated showed a reduction in the pain scale at the end of the follow-up, after a period of two weeks[7].

The search performed in the Medical Literature Analysis and Retrieval System Online (MEDLINE, via Ovid), Excerpta Medica Database (EMBASE), Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Cochrane Central Register of Controlled Trials databases did not find any studies that exclusively evaluated the effectiveness of morphine gel in malignant neoplastic wounds. Lidocaine gel at 2% is the comparator of choice, as its use is well established and supported by previous studies for the reduction of local pain[8].

The aim of the study will be to analyze the effectiveness of topical morphine in controlling local pain and promoting comfort in patients with malignant neoplastic wounds in the breast, head or neck.

METHOD

Study design

Randomized, double-blind, controlled clinical trial with exploratory allocation of 1:1, in a single center. Vital signs, functional capacity, wound staging, area and time of wound appearance, comfort, dosage of systemic morphine used and adjuvant medications will be collected in order to minimize possible confounding variables.

Study location

The study will be conducted at the National Cancer Institute, in the exclusive palliative care unit (HC IV), in the city of Rio de Janeiro, Brazil.

Eligibility criteria

Patients hospitalized with malignant neoplastic wounds in the breast or head and neck region will be included. Eligibility criteria include patients with wounds stage II or higher (Haisfield-Wolfe and Baxendale-Cox classification), of legal age, with functional capacity greater than or equal to 30% (Karnofsky Performance Status), who present local pain of, at least, three points on the numerical pain scale, ranging from zero to 10; who have been hospitalized for more than 48 hours; and are using regular systemic morphine by any route[9-10].

Patients with wounds that present fistula, extensive coagulation necrosis (greater than 50% of the area, measured according to the Pressure Ulcer Scale for Healing – PUSH scale with a disposable ruler for wound demarcation), degree of exudation greater than one (PUSH scale) and who are undergoing local radiotherapy will be excluded[11].

The research team, consisting of six nurses, two pharmacists and two physicians, ensures that all stages of the study's operational procedures are carried out. The team has received training on the complete study protocol and good clinical practices.

Interventions

Participants will be allocated to two groups that will receive: (1) treatment with morphine gel – intervention; or (2) standard treatment with lidocaine gel – control. Participants in each group will receive the treatment once a day, during the dressing procedure, and will be monitored for 3 consecutive days.

Both the morphine gel and the lidocaine gel will be prepared by a pharmacy technician in a flow hood appropriate for handling medications and then dispensed in a sterile syringe, in a box identified with the patient code and the syringes necessary for the three days of monitoring. Each syringe will have an identification label containing the term "investigational product", patient code, expiration date and study acronym.

Patients will be asked on each follow-up day about any type of reaction that may be related to the investigational product.

Patients will be discontinued due to loss of follow-up, withdrawal of informed consent, death, emergence of any exclusion criteria, mental confusion/disorientation.

Intervention group

Dimorf® (morphine sulfate) in the injectable form of 10 mg/ml will be used to prepare the gel. Curatec Hydrogel with Alginate® will be used as the base of the compound.

The morphine gel will have a proportion of 0.125%, composed of 8 g of hydrogel and 1 ml (10 mg) of morphine, and each syringe will contain 10 g of morphine gel.

Control group

The control group will receive lidocaine® gel (2% lidocaine hydrochloride in sterile jelly) alone, which has characteristics similar to the hydrogel in viscosity and transparency used in the manipulation of morphine gel, ensuring the blinding of the study.

Expected results and measurement instruments

The primary outcome will be pain intensity, measured by the Numerical Pain Rating Scale[12]. Secondary outcomes include mean pain relief, comfort measure (using the general comfort questionnaire), systemic morphine dosage (mean difference used by patients between baseline and outcome), incidence and classification of adverse events (using Common Terminology Criteria for Adverse Events - CTCAE)[13]. The design of the clinical trial and its conclusions may provide a more solid basis for the opinions of specialists who care for patients with malignant wounds. This strategy aims to help those suffering from local pain by allowing the use of a topical therapy that can potentially decrease the use of systemic opioids and their side effects.

Numerical pain rating scale

The patient reports the equivalence between the intensity of his/her pain and a numerical classification, with zero corresponding to "no pain" and 10 corresponding to "maximum pain". According to a systematic review that evaluated pain scales, they present good sensitivity and facilitate subsequent data analysis[14].

General Comfort Questionnaire

The General Comfort Questionnaire (GCQ – translated version) is a self-administered instrument that can be applied by the researcher through an interview using a Likert-type scale composed of 48 items that assess general well-being, with response alternatives ranging from one (totally disagree) to four (totally agree). The score generated by the GCQ ranges from 48 to 192 and covers comfort in the physical, psychospiritual, environmental and sociocultural contexts. The higher the scores generated, the greater the comfort felt by patients[15].

Participant Schedule

Table 1 illustrates the schedule of visits to each study participant.

Sample size

The main objective of this study was to compare the pain score before and after the intervention in each group, to verify whether there is a significant difference between the two distributions compared. Considering the ordinal nature of the variable, a confidence level of 95% and a power of 80% were set for a one-sided test, aiming to find a large effect size (at least 0.5) for the nonparametric tests. The sample size of each group was determined using the G*Power application (version 3.1.9.4), in the Wilcoxon and Mann-Whitney nonparametric test approach. The calculation suggests a minimum sample size of 106 patients (53 per arm).

Recruitment

In order to facilitate patient recruitment, hospital nurses and physicians were instructed on the study and eligibility criteria. Professionals working in the hospital pharmacy sector were instructed on the handling and dispensing flow of the products under study. An active search for patients will also be carried out by the research team. Patient recruitment began in September 2023.

Allocation

The randomization and allocation procedures will be performed using the Research Electronic Data Capture (REDCap) software on a form that will only be viewed by non-blinded members of the pharmacy team, responsible for handling the products and sending them to the team nurse who will be responsible for dressing the FNM[16-17].

Blinding

After intervention assignment, participants, caregivers, and outcome assessors will be blinded to the investigational product. The investigational products have a similar appearance, and the identified syringes have a label that covers the entire area of the syringe, preventing patients and nurses from seeing the appearance of the gel. In the event of a serious adverse event, the blinding will be broken.

Table 1 - Patient visit schedule. Niterói, RJ, Brazil, 2024

Procedures	D1[1]			D2		D3		
	Baseline[1]	After opening the dressing	After closing the dressing	BEFORE opening the dressing	AFTER opening the dressing	BEFORE opening the dressing	AFTER opening the dressing	1 hour after closing the dressing
Informed consent[2]	X							
Verification of eligibility criteria	X	X						
Physical examination								
Clinical and demographic data	X							
Randomization[3]	X							
Signs and symptoms in the wound	X	X		X	X	X	X	X
Pain Scale and General Comfort Questionnaire	X							X
Dressing[4]		X			X		X	
Vital Signs[5]	X		X			X		X
Lidocaine 2%/ Morphine[6]		X			X		X	
Collection of adverse reactions			X					X
Systemic Morphine Dosage[7]	X			X		X		
Concomitant medication	X							

Note:
1. Baseline and D1 may occur on the same day.
2. It must be signed before any study procedure.
3. Randomization will be performed by an unblinded study pharmacist only after confirmation that the patient meets the eligibility criteria.
4. Any product that is in direct contact with the wound must be removed. The wound will be cleaned with 0.9% saline solution and 2% chlorhexidine degerming agent. The dressing will be finished with a compress with petrolatum emulsion, gauze and transparent adhesive tape.
5. The visual signs will be measured before and/or after the dressing is completed.
6. Topical morphine with hydrogel base (Curatec Hydrogel with Alginate® – transparent and viscous gel) in the formulation of 10 mg of morphine sulfate intravenous solution (1 ml) with 8 g of hydrogel. The control group will receive lidocaine gel (lidocaine hydrochloride in sterile jelly at 2%).
7. The milligrams consumed by the research participant in the last 24 hours will be considered (including the regular dose and rescues administered).

Data collection methods

The data management team customized the electronic clinical record (eCRF) using the REDCap® data platform, already licensed for use at INCA.

Clinical data collection will be performed by nurses on the research team, and the entry of these data into the eCRF will be performed by the principal investigator. The principal investigator will be responsible for the accuracy and veracity of the clinical data collected at her institution and will be required to electronically sign the eCRFs when completed.

Data management

Patients are numerically coded in the data platform, as well as in the recruitment list. In addition, all procedures performed are recorded in the institution's medical record (source document), accessible to the care team, the monitoring team and the study data manager.

Statistical method

The data will be exported to the R software through API (Application Programming Interface), where the statistical analyses will be performed. The analysis will follow the intention-to-treat principles[18]. The normality of the data will be tested by visual inspection of the histograms, and the characterization of the participants will be done through descriptive statistical tests.

The differences between groups (treatment effects) and their respective 95% confidence intervals will be calculated by constructing mixed linear models, using interaction terms between treatment groups and time[19]. All analyses will be performed considering a maximum significance level of 5% and a 95% confidence interval[20-21].

Monitoring

Monitoring visits are scheduled to occur every 90 days and will be conducted independently by investigators from the clinical research and technology development division.

Ethical and regulatory aspects

The study will be conducted in accordance with the Declaration of Helsinki and Brazilian laws regulating research (Law No. 8,080, of September 19, 1990; Law No. 8,142, of December 28, 1990; and Resolution No. 466, of December 12, 2012), following good clinical practices (Good Clinical Practices – GCP).

Participants' consent will be obtained by nurses on the research team, who have been trained in accordance with good clinical practices (GCP). The data platform ensures participant confidentiality, and all participants will be informed about access to study data in their medical records and about the possibility of leaving the study by withdrawing consent, if requested by participants.

The results of the study will be published in scientific journals in the health field.

This study was approved by the Research Ethics Committees of the School of Medicine of the Fluminense Federal University (5,468,231) and the National Cancer Institute/INCA (5,588,595). It is prospectively registered in ClinicalTrials.gov (NCT05800834), version 1.0 of April 6, 2023. Any modifications will be communicated to the Research Ethics Committees, as well as to ClinicalTrials.gov.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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