Randomized Crossover Study

Morphine Versus Loperamide with Intrasite Gel in the Treatment of Painful Dermal Ulcers: A Randomized, Crossover Study

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Background: Topical morphine along with intrasite gel has been proven to be a simple and effective method to relieve pain. However, morphine is still not freely available in developing countries due to drug restrictions and stringent laws governing it. Loperamide has been reported to relieve pain caused by stomatitis effectively when given topically. Loperamide, being an mu receptor agonist with no systemic absorption, can serve a dual purpose here. Also loperamide being freely available as an over-the-counter drug can be a surrogate drug for topical application.

Objectives: The primary aim was to compare the efficacy of loperamide and morphine in treating pain when applied topically along with intrasite gel.

Study Design: Adult patients with healthy wounds with pain on Numeric Rating Scale (NRS-11) greater than 5 with no systemic comorbid illness were divided randomly into 2 groups – group morphine or group loperamide – for 24 hours followed by a 1-day washout and crossover in the other group for 24 hours. Pain was assessed once every day.

Setting: Medical college and hospital.

Methods: The parameters assessed included: (1) characteristics of the ulcer; (2) pain was assessed by NRS-11 at 12-hour intervals for a period of 72 hours; and (3) patient satisfaction. Statistical analysis used repeated measures analysis of variance to measure change in mean NRS-11 within each group. Analysis of covariance was used to compare the mean change in NRS-11 in the 2 groups.

Results: Morphine and loperamide were equivocal in pain relief after 12 and 24 hours ($P = 0.400$ and $P = 0.753$); however, the patient satisfaction scores were better in the morphine group.

Limitations: The earlier studies performed used injectable forms of morphine, for the sake of comparison, we used powdered morphine and powdered Loperamide diluted with saline. Confounding variables include ulcer size and aetiology, which can be a source of bias. The ulcer size was not standardized due to the paucity of sample to study. Equianalgesic doses of loperamide and morphine could not be found even after an extensive literature search. The loperamide dose used in our case was equal to the dose used orally since the same dose appears effective across a range of oral opioid analgesics. The morphine dose was standardized as 10 mg based on a mixture previously used to treat pain due to epidermolysis bullosa.

Conclusions: Topical loperamide can be an efficacious and novel intervention to treat painful ulcers while avoiding systemic effects.

Key words: Loperamide, morphine, painful ulcer

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Opioid receptors are found in the central nervous system (CNS) and peripheral tissues. Cutaneous ulcers are painful, affecting the quality of one's life. Systemic opioids are bound with a multitude of adverse effects adding to the already comorbid conditions of the hospice patients. Opioids

administered locally to inflammatory tissue provide good analgesia without any systemic side effects (1,2).

Platzer et al (3) state that topical peripheral application of morphine along with intrasite gel has been proven to be a simple and effective means of relieving pain (3). Loperamide has been reported to relieve pain caused by stomatitis effectively when given topically, as per the study done by Kawano (4). Loperamide has an effect on peripheral μ-opioid receptors activated by inflammation and has been investigated as a possible topical analgesic for painful ulcers of the skin or mouth (5). However, loperamide efficacy in the treatment of pain due to dermal ulcers has not been studied.

We hypothesized that loperamide being a μ receptor agonist is equally efficacious to morphine in treating pain due to cutaneous ulcers when applied locally. Although well absorbed from the gastrointestinal tract when given orally, loperamide is almost completely extracted and metabolized by cytochrome P450 in the liver, with time to peak plasma concentration of 2.5 hours, bioavailability of less than 2%, and plasma half-life of 11 hours (5). Loperamide is devoid of any side effects at normal doses but can cause QTc prolongation, ventricular arrhythmias, and CNS effects at very high doses or in those patients on drugs that inhibit human ether-a-go-go gene, such as terfenadine, cimetidine, et cetera (6,7). We planned a randomized crossover study in a pilot sample of patients with cutaneous painful ulcers to receive morphine 10 mg and loperamide 10 mg in 15 gm of Megaheal gel dressing (Aristo Pharmaceuticals Pvt Ltd., Mumbai, India).

The aim was to compare the efficacy of loperamide and morphine in treating pain when applied topically along with intrasite gel. The primary outcome of our study was to compare mean change in Numeric Rating Scale (NRS-11) score between the 2 groups, and secondary outcome being patient satisfaction.

Methods

Patients

We planned a pilot, feasibility, and crossover study over a period of 1 year in a sample of patients with cutaneous lower limb painful ulcers (NRS-11 > 5) to receive either morphine 10 mg or loperamide 10 mg in 15 gm of Megaheal gel (Aristo Pharmaceuticals) dressing. We hypothesize that loperamide is equally efficacious to morphine in treating pain due to cutaneous ulcers when applied locally. Ethical committee approval and CTRI registration of our study was done (CTRI registration number CTRI/2018/01/011621). Study protocol was in accordance with ethical standards of human experimentation.

Inclusion Criteria

Inclusion criteria included (1) age older than 18 years; (2) patients with painful cutaneous lower limb ulcers with NRS-11 score greater than 5 and size less than 20 sqcm^2; and (3) patients giving written informed consent.

Exclusion Criteria

Exclusion criteria included (1) uncooperative patients; (2) hemodynamically unstable patients, patients with liver and kidney diseases; (3) patients with unhealthy ulcers needing extensive debridement; (4) patients with allergy to any of the study drugs and intrasite formulation; and (5) patients already on oral or intravenous opioid medications.

All patients who met the inclusion criteria after giving a written, informed, valid consent were randomly allocated into either of the 2 groups by simple randomization using a computer-generated number (8). Concealment was achieved by numbering the powdered drugs to be administered. The primary consultant in charge of and who enrolled the patient, the pain physician administering the drug, and the caregivers taking the observations were blinded to the study drug being given. The patient was then treated in one group for 24 hours followed by a 1-day washout and treated in the other group for 24 hours.

Our study being a pilot and considering the high patient attrition rate in our hospital with limited available samples to choose from, a sample of 20 inpatients were considered for eligibility. All forms of intravenous and oral analgesics were withheld. The prerequisite preparation needed for study is depicted in Fig. 1.

Group Morphine

The topical morphine-intrasite gel mixture was prepared by mixing 10-mg powdered morphine tablets diluted with 5-mL saline solution with 15-g intrasite gel (Megaheal; Aristo Pharmaceuticals) in a sterile bowl. The mixture was then applied over the clean wound and further covered with simple gauze dressing.

Group Loperamide

The topical loperamide-intrasite gel mixture was prepared by mixing 10-mg loperamide tablets diluted

with 5-mL saline solution with 15-g intrasite gel (Megaheal; Aristo Pharmaceuticals) in a sterile bowl. The mixture was then applied over the clean wound and further covered with simple gauze dressing.

In our case, the loperamide dose used was equal to the dose used orally because the same dose appears effective across a range of oral opioid analgesics, as studied by Zeppetella and Ribeiro (9).

Rescue analgesic in the form of intravenous paracetamol 1 g was given if NRS-11 score was greater than 5 after 12 hours. The study was terminated if the NRS-11 score was less than 5 during the study period.

The parameters that were assessed include the following:

1. The age and gender of the patient
2. Other comorbid illness
3. Characteristics of the ulcer were noted, such as etiology, ulcer size, type, location, healing/nonhealing, and others. EPUAP- European pressure ulcer advisory panel (10) (Fig. 2)
4. Pain was assessed by NRS-11 at 12-hour intervals for a period of 72 hours
5. Patient satisfaction (yes/no) and preferred drug
6. Any rescue medication
7. Local effects
8. Systemic effects including change in hemodynamic parameters, including pulse rate, blood pressure and respiratory rate, and CNS effects, such as drowsiness, dizziness, fatigue, and others.

Fig. 1. *Prerequisite preparation.*

Grade	Description
I	Non-blanchable erythema of intact skin
II	Partial-thickness skin loss involving epidermis, dermis or both
III	Full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to, but not through, underlying fascia
IV	Full-thickness skin loss with extensive destruction, tissue necrosis, or damage to muscle, bone or supporting structures.

Fig. 2. *European pressure ulcer advisory panel grade*

Statistical analysis was done using IBM SPSS Version 20 software (IBM Corporation, Armonk, NY). Continuous variables were summarized as mean ± standard deviation (SD). Categorical variables were summarized as proportion and percentage. Mean NRS-11 was analyzed using repeated measure analysis of variance. The mean change in NRS-11 from baseline and 12 hours between the 2 groups was done using analysis of covariance using baseline as a covariate.

Following the completion of the study, the patient continued to be treated with the topical medication he or she preferred.

Results

Thirteen patients who met the inclusion criteria of the crossover study were randomly allocated into study groups. One patient was excluded from the study due to loss to follow-up (CONSORT Statement, Fig. 3). Three patients could not be crossed as the NRS-11 score was less than 5 after washout, leading to missing data in 2 patients in the loperamide group and one patient in the morphine group. Figure 4 depicts a few of the ulcers treated in our study.

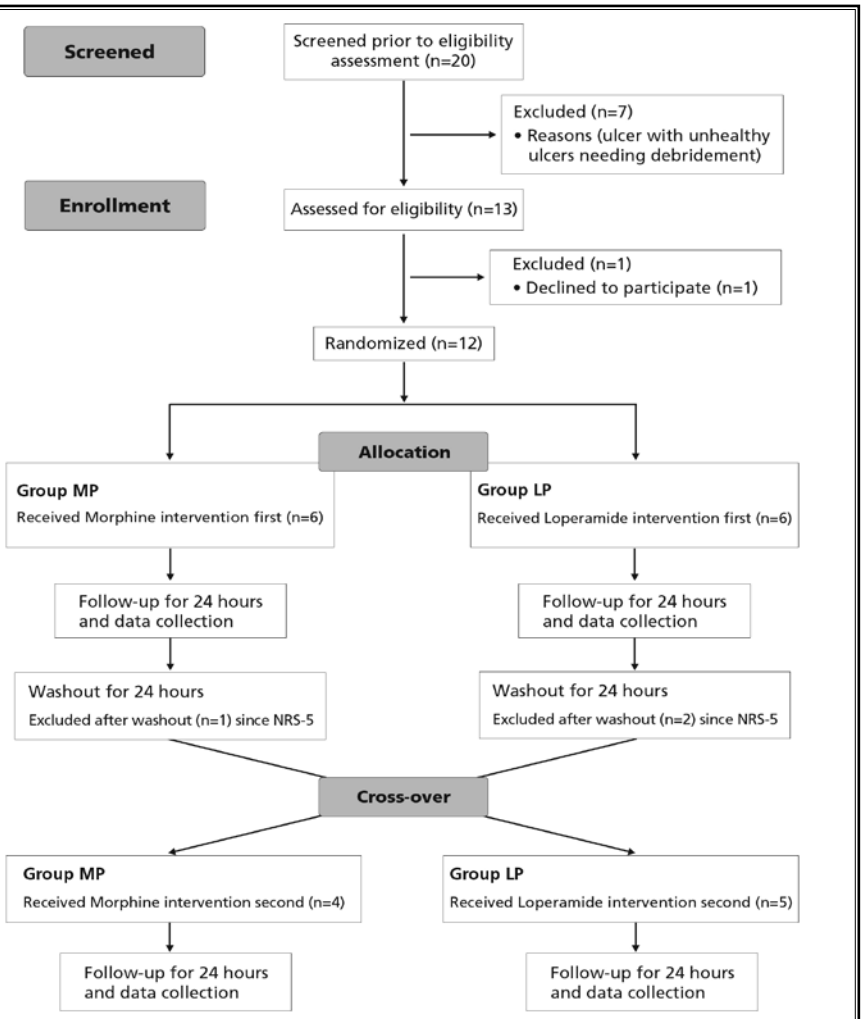

Fig. 3. *CONSORT flow diagram.*

Table 1 shows the baseline demographics and clinical characteristics of the patients. Data assayed revealed the mean ulcer size 59.67 cm^2 with many outliers. Some 66.7%, that is, 8 patients had European Pressure Ulcer Advisory Panel score of III; 25%, that is, 3 patients had score of II; and 8.33%, that is, one patient had a score of IV. The mean NRS-11 score of the 12 patients at baseline was 7.58 ± 1.51.

Comparison of mean NRS-11 scores of morphine and loperamide at baseline, 12 hours, and 24 hours showed significant reduction in NRS-11 scores (morphine $P = 0.001$, loperamide $P = 0.049$; Tables 2 and 3; Fig. 5); however, no significant difference in mean NRS-11 scores were noted while comparing 12 and 24 hours.

Comparison in mean change in NRS-11 scores between the 2 groups was done using univariate analysis of variance with baseline as covariate. There was no significant difference in the mean change at 12 hours ($F = 0.744$, $P = 0.400$) and 24 hours ($F = 0.102$, $P = 0.753$) between the 2 groups (Tables 4 and 5).

Five patients preferred morphine as an analgesic, 2 patients preferred loperamide, and 2 patients said both the drugs were equally efficacious. Pruritus, although present, was not so troublesome.

Discussion

Stein (11) states that opioid antinociception can be initiated by activation of opioid receptors located outside the CNS. Our study has been able to estimate the role of loperamide and morphine as opioids in treating pain due to cutaneous ulcers. The presence of inflammation has proven to be ofcrucial importance for the manifestation of peripheral opioid antinociceptive effects.

Morphine has already proven itself to have an analgesic effect when applied topically for benign and malignant ulcers, as per the earliest studies by Wood (2). A double-blind, randomized study in 16 patients found significantly lower NRS-11 scores in morphine compared with placebo. Our study validates the previous studies showing morphine being a potent topical analgesic (9).

However, morphine is still not freely available in developing countries due to drug restrictions and stringent laws governing it. In the United States, 55,704 mg of morphine was available to each patient with palliative care needs, meeting that need by more than 30 times. In 2015 in India, only 43 mg were available per patient, meaning that the opioid medication available in the country was sufficient to meet just 4% of the need (12).

Stein (11) also mentions that the direct local

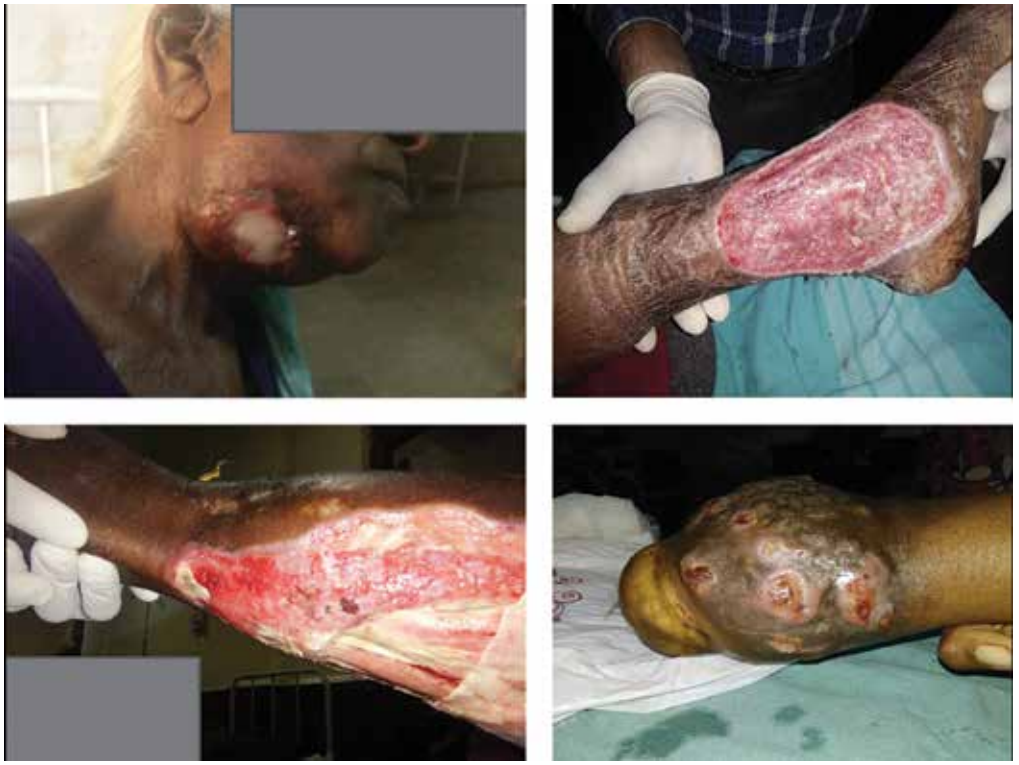

Fig. 4. *Few ulcers of our study.*

Table 1. *Demographic details with baseline NRS-11.*

Number of Patients	12
Age in Years (Mean ± SD)	48.08 ± 17.97
Gender	
Male	10 (83%)
Female	2 (17%)
Weight in kg (Mean ± SD)	54.67 ± 6.72
Wound Etiology	
Posttraumatic	2 (16.67)
Buccal mucosa carcinoma	2 (16.67)
Traumatic injury	2 (16.67)
Cellulitis	4 (33.33)
Ca cheek	1 (8.33)
Marjolin ulcer	1 (8.33)
Ulcer size in SqCm	
Mean ± SD	59.67 ± 72.04
Median (IQR)	40 (16.25-61.5)
Baseline NRS-11	
Mean ± SD	59.67 ± 72.04
Median (IQR)	7.5 (6.25-9.0)

IQR, interquartile range.

Table 2. *Comparison of mean NRS-11 with morphine at different follow-up time.*

Morphine (NRS-11)	n	Mean	SD	Median (IQR)	Repeated Measures Analysis of Variance
Baseline	10	7.7	1.64	8 (6-9)	$F = 25.64$ $P = 0.001$
12 hrs	10	5.5	1.63	5.25 (5-6)	
24 hrs	10	5.4	1.76	5.25 (5-6)	

IQR, interquartile range.

Table 3. *Comparison of mean NRS-11 with loperamide at different follow-up time.*

Loperamide (NRS-11)	n	Mean	SD	Median (IQR)	Repeated Measures Analysis of Variance
Baseline	11	7.41	1.69	7 (6-9)	$F = 3.52$ $P = 0.049$
12 hrs	11	6.05	2.17	7 (5-7)	
24 hrs	11	5.59	1.8	5.5 (5-7)	

IQR, interquartile range.

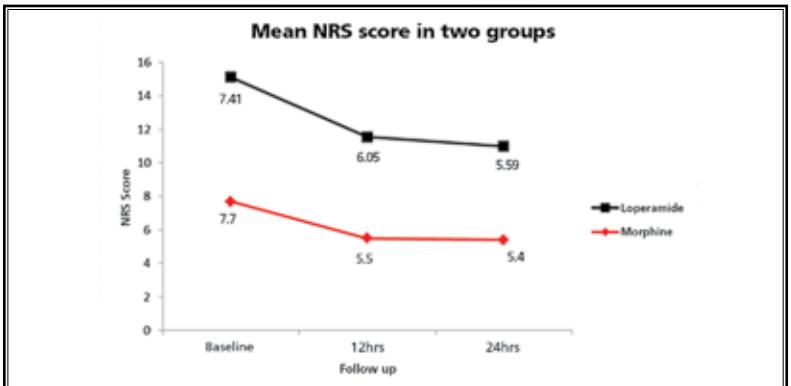

Fig. 5. *Comparison of mean NRS-11 scores of Group MP and Group LP.*

Table 4. *Estimated means using univariate analysis of variance at 12 hours.*

Pairwise Comparisons
Dependent Variable: Pain Score 12 hrs

(I) Group	(J) Group	Mean Difference (I-J)	Standard Error	Sig. *	95% Confidence Interval for Difference	
					Lower Bound	Upper Bound
Morphine	Loperamide	-0.686	0.795	0.400	-2.355	0.984
Loperamide	Morphine	0.686	0.795	0.400	-0.984	2.355

Based on estimated marginal means.
*Adjusted for multiple comparisons: Bonferroni.

Table 5. *Estimated means using univariate analysis of variance at 24 hours.*

Pairwise Comparisons
Dependent Variable: Pain Score 24 hrs

(I) Group	(J) Group	Mean Difference (I-J)	Standard Error	Sig. *	95% Confidence Interval for Difference[a]	
					Lower Bound	Upper Bound
Morphine	Loperamide	-0.252	0.788	0.753	-1.907	1.402
Loperamide	Morphine	0.252	0.788	0.753	-1.402	1.907

Based on estimated marginal means.
*Adjusted for multiple comparisons: Bonferroni.

application of small, systemically inactive, that is, lipophobic, doses of agonists in clinical situations of inflammatory pain may be particularly rewarding to study.

Loperamide being an mu receptor agonist and synthetic analog of pethidine can serve a dual purpose in this scenario. Loperamide is an opioid analog with peripheral mu opioid with additional weak anticholinergic activity used primarily as a constipating agent, more potent than codeine (13). Little is absorbed from the intestines, and entry into brain is negligible. Loperamide has been used as a pain killer for cancer treatment–induced oral mucositis (14). Also, because loperamide is freely available as an over-the-counter drug and an inexpensive antidiarrheal drug, we considered it as an ideal drug for topical application. Our study was able to confirm its potency as a topical analgesic and equianalgesic to morphine. However, it requires further studies to estimate the loperamide potential analgesic dose.

Loperamide was able to cause significant reduction in the mean NRS-11 scores in the first 12 hours. Our study validates the analgesic efficacy of loperamide topically. Standardized loperamide emulsions can be prepared as an analgesic mixture to apply over unhealed wounds in the future. We suggest further trials to assess the untapped potential of loperamide. The results, although equivocal, need higher sample size to confirm the results.

The NRS-11 pain scores continued to be significantly decreased during the first 12 hours of washout (P = 0.017), which increased during the next 12 hours (P = 0.057). This could probably be attributed to the little systemic absorption of loperamide compared with morphine even after 3 times duration of half-life has passed (15).

None of the patients needed rescue analgesia due to breakthrough pain. However, one patient received paracetamol for fever. This again rubberstamps the potency of topically applied intrasite gel mixed with opioids.

One patient after morphine application complained of itching, whereas 3 patients complained the same after loperamide. This pruritus could be attributed to activation of "itch-selective" neurons at the spinal level. Studies suggest that opioids can also induce itching at the spinal level by "itch-selective" secondary neurons in the lamina I of spinothalamic tract of the dorsal horn. The reasons for pruritus have been still speculative, and spinal triggering of itching is observed in particular by

activation of μ-opioid receptors (16). Future topical studies could elucidate the reasons of itching. This partly explains the fact that systemic absorption is significantly higher with morphine, and loperamide can serve as a surrogate here. Morphine being systemically absorbed can also cause sedation, as noted in one of our patients.

No side effects, such as pruritis, CNS effects, or addiction, were noted in patients on loperamide. Loperamide is a P-glycoprotein substrate and efflux pumps in enterocytes and the CNS lead to low bioavailability and poor penetration through the blood–brain barrier. As a result, loperamide does not cause analgesia, euphoria, or respiratory depression at usual doses used orally, that is, 16 mg or less in 24 hours (6). Doses used in our study (10 mg topically) were significantly less to cause any CNS effects or abuse.

Morphine performed better than loperamide in decreasing pain scores, and the patient satisfaction was better. The difference in the potency of the drug could be attributed to a priori to differing analgesic doses of the 2 drugs.

There were several limitations of our study, which could not be addressed due to practical reasons. (1) The earlier studies performed have used injectable forms of morphine. For the sake of comparison, we used powdered morphine and powdered loperamide diluted with saline solution. (2) Cofounding variables include ulcer size and etiology, which can be a source of bias. The ulcer size was not standardized owing to the paucity of sample to study. (3) Equianalgesic doses of loperamide and morphine could not be found even after extensive literature search. In our case, loperamide dose used was equal to dose used orally because the same dose appears effective across a range of oral opioid analgesics. Morphine dose was standardized as 10 mg based on a mixture previously used to treat pain due to epidermolysis bullosa.

Our study revisits peripheral action of opioids to relieve pain. Graham et al (17) suggest that current unpublished guidance reveals different practices indicating the need to work toward an international consensus for the administration of topical opioids.

Conclusions

Loperamide with intrasite gel can be an exciting, efficacious, and a novel intervention to treat pain due to cutaneous ulcers when applied topically avoiding systemic effects. Pruritus, although present, is not so troublesome. Topical morphine with intrasite gel is more potent and efficacious but underutilized heretofore for pain management. Multicentric, large sample studies need to be planned with involvement of government pharmacologic agencies that will prepare standardized mixtures of opioids for topical use that can alleviate the pain of many.

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