Research Paper

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Efficacy and safety of loxoprofen sodium topical patch for the treatment of pain in patients with minor acute traumatic limb injuries in Brazil: a randomized, double-blind, noninferiority trial

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Abstract

Posttraumatic injury pain is commonly treated with oral nonsteroidal anti-inflammatory drugs. However, oral nonsteroidal anti-inflammatory drugs cause several adverse events, with topical formulations arising as an important alternative. Therefore, we aimed at evaluating the efficacy and safety of loxoprofen patch (LX-P) in the treatment of patients with posttraumatic pain. This phase III, randomized, double-blind, noninferiority study enrolled Brazilian patients aged 18 to 65 years diagnosed with lower and upper limb posttraumatic injury who were experiencing moderate or severe pain. Patients were assigned to active LX-P or to loxoprofen tablet (LX-T), and pain intensity was measured based on a visual analog scale score variation after 7 days of treatment. Data on clinical symptoms, rescue medication use, and adverse events were also collected. Visual analog scale score variation was compared using a 10% noninferiority margin. Two hundred forty-two patients were randomly assigned to LX-P (n = 123) or to LX-T (n = 119). The results showed a reduction in pain after 7 days of treatment: −49.96 (n = 118; SE 1.7) in the LX-P and −47.71 (n = 117; SE 1.6) in the LX-T groups (difference of −2.25; 95% CI: −5.97 to 1.47; $P = 0.23$). On the safety analysis, the LX-T group presented twice as many patients with treatment-emergent adverse events as the LX-P group (30.8% and 14.2%, respectively). A sensitivity analysis demonstrated that rescue medication use has not affected the primary end point. This study showed that LX-P has a comparable efficacy to LX-T, but with a better safety profile, being a therapeutic option for the treatment of posttraumatic injury pain.

Keywords: Loxoprofen, Nonsteroidal anti-inflammatory drugs, Pain, Injuries, Topical anti-inflammatory drug

1. Introduction

Pain is one of the major consequences of the inflammatory process, often resulting in anti-inflammatory drug administration. In posttraumatic injuries (musculoskeletal and soft tissue injuries, including sprains, distensions, and contusions), cell damage occurs when a mechanical load exceeds the tissue strength, leading to an inflammatory process.[6] This kind of lesion is usually related to sports' practice.[16,19]

The administration of nonsteroidal anti-inflammatory drugs (NSAIDs) is indicated to manage posttraumatic injury symptoms, including pain. However, the use of oral NSAIDs has been associated with gastrointestinal, cardiovascular, and renal adverse events.[7,26] Traditional NSAIDs inhibit cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes, leading to a reduction in the prostaglandin levels. Thus, they carry a higher risk of upper gastrointestinal complications, such as erosive gastritis and bleeding, as shown in a recent meta-analysis of NSAIDs' clinical trials.[31] Moreover, 30% to 50% of chronic NSAID users have endoscopic lesions (eg, subepithelial hemorrhages, erosions, and ulcerations), often with no clinical symptoms.[27]

The topical formulation emerged as an alternative to oral NSAIDs. This type of formulation provides a similar efficacy profile compared with the oral drugs with a significant reduction in NSAID-related adverse events.[25] Loxoprofen is a prodrug that, after conversion to its transalcohol metabolite, suppresses the prostaglandin biosynthesis through nonselective inhibition of COX enzymes.[14] Among the topical formulations, the loxoprofen hydrogel patch, and its bioequivalent formulation—loxoprofen tape, allows the direct penetration of loxoprofen into the affected site providing prolonged pain relief. Studies have shown that the topical formulation is effective and well tolerated for the treatment of pain and inflammation.[14] Of note, in a study conducted in Japan, the topical formulation was noninferior to loxoprofen tablets (LX-T) in reducing posttraumatic pain and swelling and with a similar safety profile.[28]

The current study aimed at evaluating the efficacy and safety of a new loxoprofen nonhydrogel patch (LX-P) in the treatment of patients with moderate or severe posttraumatic pain.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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2. Methods

We conducted a phase III, parallel, randomized, double-blind, double-dummy, noninferiority comparative trial that evaluated the efficacy and safety of LX-P vs LX-T in patients with a recent (48 hours before the baseline visit) posttraumatic injury. Patients were recruited from 8 Brazilian sites (both emergency and outpatient care settings) in southeast, midwest, and northeast geographic regions, from November 2015 to January 2017. The recruitment setting for each site was not documented.

The study was conducted according to the Guideline for Good Clinical Practice of the International Conference on Harmonization (ICH-GCP) and the Brazilian regulations. The study was approved by the ethics committees of each site and by the National Committee for Ethics in Research (CONEP/CNS/MS), and it was registered in clinicaltrials.gov (NCT02616068).

2.1. Participants

Patients were considered eligible if they were aged 18 to 65 years and had recent (48 hours before the baseline visit) posttraumatic disease (contusion or sprain) of lower or upper limbs, with at least 1 moderate to severe symptom of pain or inflammation, according to the investigator's evaluation. Patients with posttraumatic disease in the finger and/or toes were excluded because of the small affected area to administer the patch. Patients were also excluded if they had cardiovascular, renal, or hematological disease, diabetes mellitus, gastrointestinal disease, hepatic disease, asthma, rheumatoid arthritis, osteoarthritis, or any other serious chronic comorbidity (at the investigator's discretion); had a previous history of gastrointestinal bleeding or ulcers (6 months before enrollment in the study); had any hemorrhagic disorder; had apparent complication of bacterial infection; had a fracture or need of immobilization with cast or surgical procedure or neck sprain; had skin sores in the application site; had bad or sensitive condition of the skin with previous history of dermatitis due to the use of topic drugs; had made a previous (5 days before the study treatment was initiated) or current use of pain medications, NSAIDs, anti-inflammatory drugs, or steroids; and had a known allergy to loxoprofen, inactive ingredients of the formulation, or any other NSAIDs. Subjects who were pregnant or breastfeeding, those who wanted to become pregnant, or who refused to use a safe birth control method during the study and subjects who had participated in another clinical study in the last 12 months were also excluded. All patients provided written informed consent.

2.2. Interventions

The investigators were allowed a maximum of 24 hours, from the screening visit, to randomize the subjects. This time frame allowed for laboratory results and other screening assessments to be completed according to the protocol. The subjects were randomized via an Interactive Web Randomization System and started treatment as soon as screening procedures were completed and eligibility confirmed. Patients were stratified by the Interactive Web Randomization System according to the pain level at baseline (moderate or severe, according to the investigator's judgment) and by the recruiting site. Patients were assigned in a 1:1 ratio to receive oral loxoprofen sodium at a dose of 60 mg 3 times a day, preferably after a meal, combined with placebo topical patch applied on the injury site once daily (LX-T group) or loxoprofen sodium by the topical route at a dose of 100 mg combined with a placebo tablet (LX-P group). Treatment assignment was done according to a predetermined blinded randomization schedule by a member who was not involved with the care of subjects. The investigator and his team, the sponsor, and the research subjects were blinded to treatment allocation, and the study drug was provided packed to be taken at home, and it was not possible to distinguish the placebo from active treatment. All study drugs were provided to sites by Daiichi Sankyo do Brasil Farmacêutica Ltda, Barueri, Brazil.

Rescue medication use was allowed (acetaminophen 750 mg up to 4 times/day) if pain relief was not achieved by the study medication or to alleviate relevant adverse events. Compliance to experimental drug and rescue medications was assessed by package return, medication count, and patient's diary on each visit.

2.3. Sample size

A literature review was conducted to estimate the minimum clinically relevant difference in clinical trials involving the experience of pain,[13,24,30] and the sample size was calculated using PASS software (2011 version). A 1-sided type I error of 2.5%, an SD inferior to 25% on each group, and a noninferiority margin of 10% (or 10 mm) were considered for the sample size estimation. It was established that 120 participants in each group would provide 80% power to demonstrate noninferiority of the loxoprofen patch compared with the oral formulation, considering a dropout rate of 20%.

2.4. End points

The primary end point was the mean change in the level of pain, based on a validated visual analog scale (VAS) score, completed by the patient. Patients were oriented to complete the score based on their pain level at the time of the questionnaire during each study visit. The VAS score is a validated and reliable unidimensional measure for acute pain.[4,5,12] Change in the score of spontaneous pain was defined as the difference between the baseline score and the score after 7 days of treatment (day 8, visit 2). The VAS for pain comprised a 100-mm line, with 0 representing the absence of pain and 10 representing disabling pain. The score was determined by the distance (mm) between zero and the patient's mark.

The secondary end points included a change in the severity of pain according to the VAS score after 3 days of treatment (day 4, visit 1), clinical symptoms assessed by the investigator (pain, inflammatory symptoms, and mobility limitation assessment using a 4-point scale on day 4 and day 8, with the following categories: 0 = asymptomatic, 1 = medium, 2 = moderate, and 3 = serious), and patients' impression on study treatment (7-point scale on day 4 and day 8, with the following categories: 1 = extremely good, 2 = good, 3 = slightly good, 4 = it has not changed, 5 = slightly bad, 6 = bad, and 7 = extremely bad). Patients were grouped according to their assessment of treatment satisfaction into groups 1 to 2, groups 3 to 5, and groups 6 to 7. The proportion of responders to treatment (responders were defined as the patients who achieved scores 0-2 in the VAS in the last visit) and the use of rescue medication (assessed based on the patient's diary and accountability of drugs returned) were also

determined. Safety was evaluated during the study visits by physical examinations, vital signs, laboratory tests, assessment of pain, and clinical symptoms. Data on the use of concomitant drugs and the occurrence of treatment-emergent adverse events (TEAEs) were also collected. TEAEs were defined as all adverse events occurring or worsening after study drug initiation. All data related to efficacy and safety assessments were recorded during visits 1 and 2. An electronic case report form specially designed for this study was used for storage and retrieval of data.

2.5. Statistical analysis

The primary efficacy end point was analyzed in the intention-to-treat (ITT) and per-protocol (PP) populations. The ITT population included all randomized patients who received at least 1 administration of the study drug and for whom at least 1 baseline and 1 post-baseline efficacy assessment were available. The PP population included all patients who completed the study according to the protocol and who had no significant protocol deviations. The safety analysis set comprised all patients who received at least 1 administration of the study medication.

Descriptive statistics were used to characterize the demographic and clinical characteristics of the patients. The mean, SD, minimum, maximum, median, and interquartile range summarized the continuous variables. Simple and crossed contingency tables described categorical variables, with frequencies and absolute percentages with 95% confidence interval (CI). Missing data were not imputed. To compensate for the missing data, we used the mixed model for repeated measures to analyze the primary end point. An unstructured within-subject correlation structure was used for the covariance matrix, and the Kenward–Roger approximation was used to estimate denominator degrees of freedom. The residual/restricted maximum likelihood method was used to estimate parameters. The null hypothesis was rejected if the upper limit of the 95% CI was less than 10%.

A sensitivity analysis was performed to confirm that the primary end point was not affected by the use of rescue medication. Patients who used rescue medication after day 4 were excluded from this analysis, and a mixed model for repeated measures was also used. Responders were defined as subjects with a response indicated in the mild section of the VAS image. The number needed to treat (NNT) of response to treatment and to prevent gastrointestinal adverse event (NNTp) were calculated for efficacy and safety analysis, respectively. The NNT for the proportion of responders was calculated in the ITT and PP populations, based on the absolute risk difference between the LX-P and LX-T groups. The NNTp concept was used in the number of patients presenting gastrointestinal TEAEs. It was calculated in the ITT safety population, based on the absolute risk difference of gastrointestinal TEAEs in the LX-P and LX-T groups. All statistical analyses were conducted using SAS version 9.4 software.

3. Results

3.1. Patients

Between November 2015 and January 2017, 254 patients were screened, and 242 eligible patients were randomized to the experimental (LX-P, n = 123) and to the control (LX-T, n = 119) groups. A total of 237 patients were included in the ITT population (LX-P n = 120 and LX-T, n = 117), and 207 were included in the PP population (LX-P n = 109 and LX-T, n = 98).

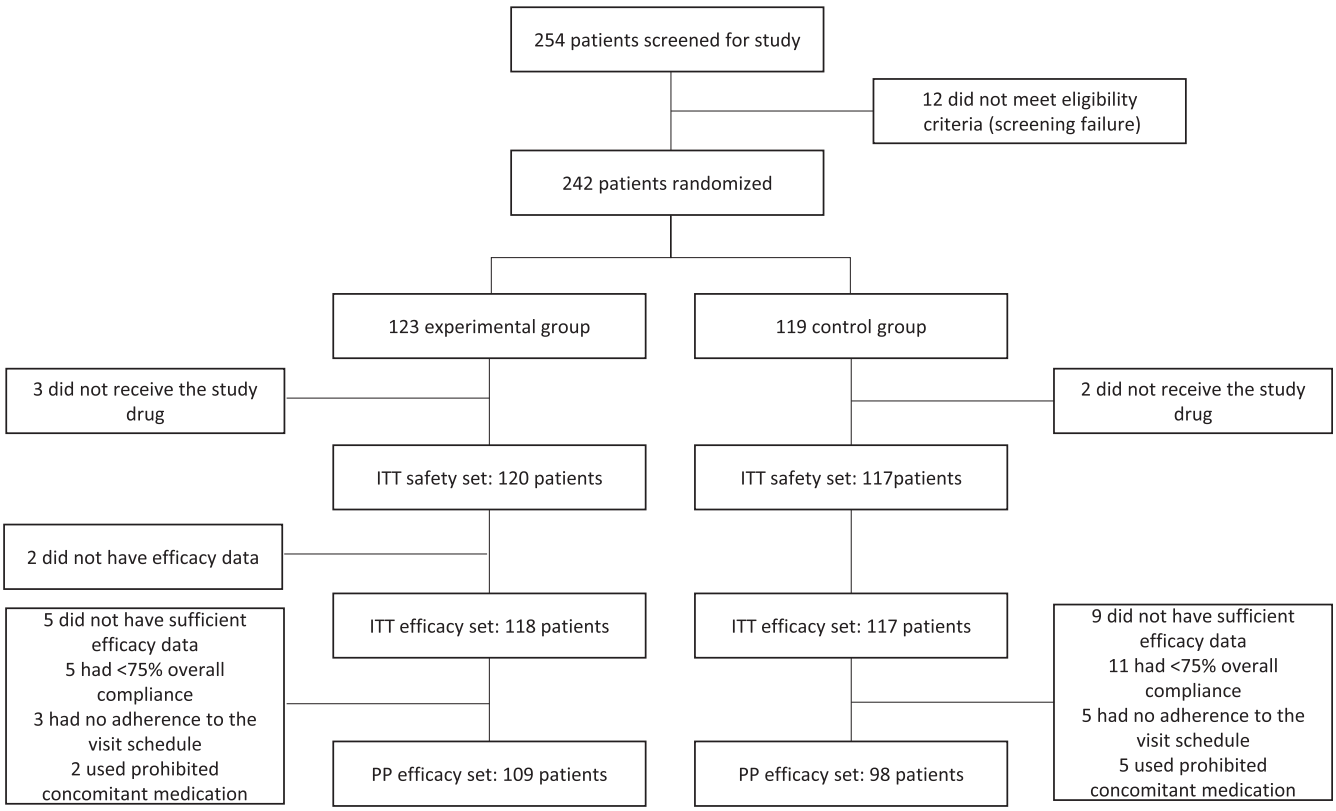

Figure 1. Consort flowchart. ITT, intention to treat; PP, per protocol.

Patients who used prohibited concomitant medication, including prohibited analgesic drugs, were excluded from the PP population (**Fig. 1**).

The mean (SD) age at screening was 35.7 (12.2) years. Slightly more women (n = 131, 55.3%) and whites (n = 121, 51.5%) were enrolled. Overall, the demographic and clinical characteristics of the randomized patients were similar at baseline except for hypertension, which was more common in the experimental group (**Tables 1 and 2**). All patients included in the PP population were compliant to the study treatment. In the ITT population, most patients were compliant to the study treatment, ranging from 90% to 95% (supplementary material, available at http://links.lww.com/PAIN/A767).

3.2. Primary efficacy end points

In the ITT population, the least square mean (LSM) change in the VAS from baseline was −49.96 mm (n = 118; SE 1.7) in the LX-P group and −47.71 mm (n = 117; SE 1.6 mm) in the LX-T group (difference of −2.25 mm; 95% CI: −5.97 to 1.47 mm; $P = 0.234$). A similar result was found in the PP population (−50.47 mm, n = 109; SE 1.7 mm for the LX-P group and −48.11 mm, n = 98; SE 1.7 mm for the LX-T group; difference −2.36 mm; 95% CI: −6.16 to 1.45 mm; $P = 0.223$). Noninferiority was demonstrated for both population analysis sets (**Fig. 2**). No differences were observed in the subgroup analysis based on pain level and site stratification (data not shown). In the ITT population, 88.7% and 82.3% of the patients were considered responders in the LX-P and LX-T groups, respectively. Similar results were observed in the PP population (89% and 81.6% for LX-P and LX-T, respectively).

3.3. Secondary efficacy end points

From baseline to day 4, the LSM change in the VAS was −29.37 mm (n = 116; SE 1.95 mm) in the LX-P group and −31.28 mm (n = 116; SE 1.90 mm) in the LX-T group (difference 1.91 mm; 95% CI: −2.41 to 6.23 mm; $P = 0.383$, ITT population). Similar results were observed in the PP analysis (−29.90 mm, n = 107; SE 2.01 and −30.44 mm, n = 98; SE 2.05 mm [difference 0.54 mm; 95% CI: −3.94 to 5.03 mm; $P = 0.811$] in the experimental and control groups, respectively).

Patients' impression of the treatment showed a difference ($P = 0.0418$) on day 4; the experimental active patch had lower proportions of subjects in groups 1 to 2 compared with the Control Active Tablet (80.6% and 89.8%, respectively). However, no statistically significant difference was observed on day 8, and the majority of subjects were included in groups 1 to 2 (94.5% and 94.9%, experimental active patch and control active tablet, respectively). In addition, clinical symptoms were similar between groups according to each visit assessment,

Table 1

Demographic characteristics of the patients.

Characteristic	ITT safety population		
	LX-P (n = 120)	LX-T (n = 117)	Total (N = 237)
Age (y)	36.7 ± 12.7	34.8 ± 11.6	35.7 ± 12.2
Women, n (%)	70 (58.3)	61 (52.1)	131 (55.3)
BMI (kg/m^2, mean, SD)	26.97 (5.36)	26.02 (4.62)	
Race group, n (%)			
White	58 (48.7)	63 (54.3)	121 (51.5)
Black	18 (15.1)	16 (13.8)	34 (14.5)
Brown	16 (13.4)	14 (12.1)	30 (12.8)
Asian	1 (0.8)	0	1 (0.4)
Other	26 (21.8)	23 (19.8)	49 (20.9)
Missing	1	1	2
Ethnicity, n (%)			
Hispanic or Latino	60 (50.8)	61 (53.0)	121 (51.9)
Non-Hispanic or Latino	58 (49.2)	54 (47.0)	112 (48.1)
Missing	2	2	4
Subjects with at least 1 medical history condition, n (%)	41 (34.2)	32 (27.4)	73 (30.8)
Hypertension	10 (8.3)	3 (2.6)	13 (5.5)
Metabolic and nutrition disorders	4 (3.3)	4 (3.4)	8 (3.4)
Musculoskeletal and connective tissue disorders	4 (3.3)	4 (3.4)	8 (3.4)
Neoplasms benign, malignant, and unspecified	4 (3.3)	2 (1.7)	6 (2.5)
Gastrointestinal disorders	2 (1.7)	2 (1.7)	4 (1.7)
Respiratory disorders	1 (0.8)	2 (1.7)	3 (1.3)
Renal and urinary disorders	1 (0.8)	1 (0.9)	2 (0.8)
Cardiac disorders	0	1 (0.9)	1 (0.4)
Subjects with at least 1 concomitant medication, n (%)	43 (35.8)	47 (40.2)	90 (38.0)
Analgesics	4 (3.3)	5 (4.3)	9 (3.8)
Drugs for acid-related disorders	2 (1.7)	4 (3.4)	6 (2.5)
Drugs for obstructive airway diseases	1 (0.8)	2 (1.7)	3 (1.3)
Antithrombotic agents	1 (0.8)	0	1 (0.4)

BMI, body mass index; ITT, intention to treat; LX-P, loxoprofen patch; LX-T, loxoprofen tablet.

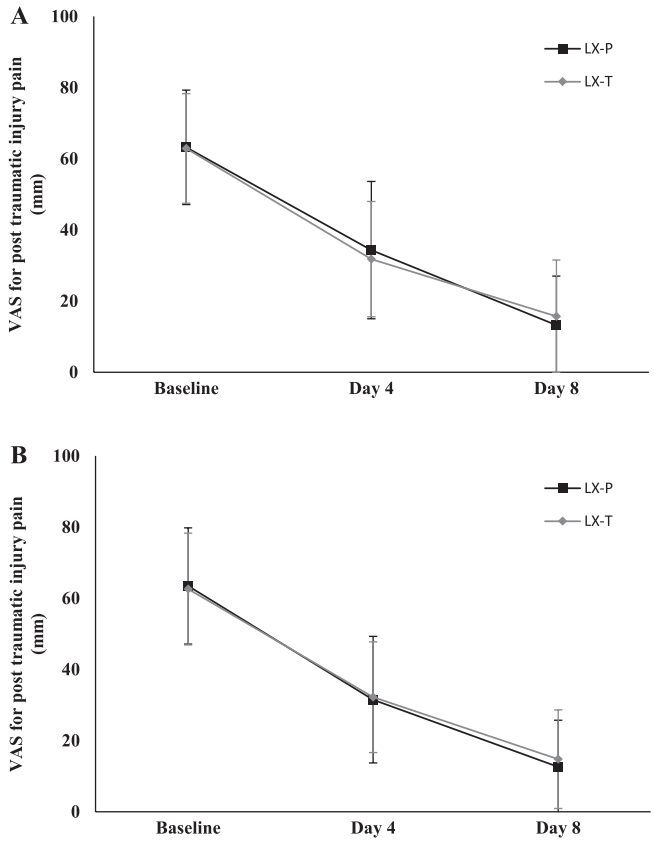

Figure 2. Change in the VAS score from baseline to day 4 (3 days of treatment) and day 8 (after 7 days of treatment). Data are presented as mean and SD (error bars). (A) Corresponds to the ITT efficacy population and (B) to the PP efficacy population. LX-P, loxoprofen patch group; LX-T, loxoprofen tablet group; PP, per protocol; VAS, visual analogue scale.

both in ITT and PP populations. In general, most subjects presented moderate (score 2) pain intensity, inflammation, and mobility limitation at baseline, changing to asymptomatic (score 0) at the last visit (day 8), on both ITT and PP populations (supplementary material, available at http://links.lww.com/PAIN/A767). The proportion of responders in LX-P and LX-T of the PP population was 89% and 81.6%, respectively ($P = 0.119$; $NNT_{PP} = 14$). In the ITT population, the proportion of responders was 88.7% and 82.3% in the LX-P and LX-T groups, respectively ($P = 0.153$; $NNT_{ITT} = 15$).

We observed a statistically significant difference ($P = 0.038$) in the use of rescue medication between study arms (13/109 vs 4/98 in the LX-P and LX-T groups, respectively). In the sensitivity post hoc analysis, it was demonstrated that the primary efficacy end point was not affected by the rescue medication use. The difference between LSM change in the VAS between the LX-P and the LX-T groups was −2.34 mm (95% CI: −6 to 1.315 mm; $P = 0.208$, PP population).

3.4. Safety

The incidence of TEAEs during the study was lower in the experimental group, as shown in **Table 3**. No severe TEAEs were reported in this study.

In general, gastrointestinal-related adverse events were more common in the LX-T than in the LX-P group (12.8% vs 0.8%, respectively. $NNT_{ITT} = 8$). Administration site–related adverse events were similar between experimental and control groups (5.0% and 6.8%, respectively) (**Table 3**).

4. Discussion

Oral NSAIDs have been the mainstay treatment for acute injury because of their analgesic and anti-inflammatory effects, but their use has been related to a high incidence of adverse events. This study showed that the topical formulation of loxoprofen (LX-P) was not inferior to the oral formulation (LX-T) in the treatment of traumatic injury pain in both ITT and PP analyses.

In general, oral NSAIDs act by inhibiting the COX isoenzymes, reducing the levels of prostaglandin and, consequently, the level of inflammation and pain intensity.[20] To provide symptomatic pain relief, oral NSAIDs must achieve systemic efficacy levels, which also causes several complications.[20] For this reason, topical formulations have been used as an important alternative to oral NSAIDs. Topical formulations provide low drug systemic levels as they produce peak plasma levels of less than 10% of those observed after oral NSAID administration.[18] Nevertheless, they are still as efficacious as the oral formulation. A review investigating topical NSAIDs in the United States concluded that these topical formulations are beneficial both from a therapeutic and from a tolerability perspective.[22] In addition, a systematic review and meta-analysis assessing 25 studies on topical NSAIDs confirmed that this administration form was effective and safe in treating chronic musculoskeletal conditions for 2 weeks.[21]

Topical loxoprofen has proven to be efficacious and safe in the management of pain in other studies. For instance, one of the studies showed that topical loxoprofen was noninferior to oral loxoprofen in improving by at least 50% each of 7 main symptoms in patients with knee osteoarthritis.[23] In addition, topical loxoprofen is also comparable to other topical therapies available for the management of pain; a study assessing loxoprofen patches showed that VAS scores were significantly lower in 50% of patients who switched from other topical NSAIDs to topical loxoprofen after 1 week of application.[2] Moreover, an open-label noninferiority trial showed that loxoprofen patch was noninferior to ketoprofen patch in the overall improvement of symptoms in patients with osteoarthritis after 4 weeks of treatment.[14] These data corroborate our results, supporting LX-P as an efficacious alternative to LX-T and other topical therapies.

According to our results, there were more subjects who used at least 1 dose of the rescue medication in the LX-P group ($P = 0.0378$). Although only a small number of patients in the study used acetaminophen, this difference could indicate that the efficacy results would possibly be associated with the use of rescue medication. Thus, we conducted an additional efficacy analysis excluding patients who used rescue medication after day 4. There is evidence in the literature showing that acetaminophen has a central mechanism of action, with poor ability to inhibit peripheral COX isoforms.[1] In addition, acetaminophen half-life is estimated to be 2 to 3 hours. Therefore, considering the acetaminophen's pharmacodynamic and pharmacokinetic profiles, the exclusion of patients using the rescue medication after day 4 mitigates interferences in the VAS score on day 8. This post hoc analysis confirmed noninferiority of the LX-P compared with the oral formulation.

Besides VAS score changes, LX-P also showed comparable results on secondary end points. Patients from both groups presented a similar reduction in pain, inflammation, and mobility limitations, as assessed by the investigators, changing from moderate pain to asymptomatic. Although the VAS score change is a reliable tool for assessing pain intensity, it is still limited

Table 2

Baseline clinical characteristics of the patients.

Parameter	ITT safety population			PP efficacy population		
	LX-P (n = 120)	LX-T (n = 117)	Total (N = 237)	LX-P (n = 109)	LX-T (n = 98)	Total (N = 207)
Posttraumatic disease, n (%)						
Contusion	70 (58.3)	64 (54.7)	134 (56.5)	61 (56.0)	51 (52.0)	112 (54.1)
Sprain	49 (40.8)	53 (45.3)	102 (43.0)	47 (43.1)	47 (48.0)	94 (45.4)
Contusion + sprain	1 (0.8)	0	1 (0.4)	1 (0.9)	0	1 (0.5)
Pain severity, n (%)						
Moderate	94 (78.3)	90 (76.9)	184 (77.6)	86 (78.9)	78 (79.6)	164 (79.2)
Severe	26 (21.7)	27 (23.1)	53 (22.4)	23 (21.1)	20 (20.4)	43 (20.8)
Clinical symptoms, n (%)						
Pain						
Medium (grade 1)	2 (1.7)	2 (1.7)	4 (1.7)	0	1 (1.0)	1 (0.5)
Moderate (grade 2)	92 (76.7)	88 (75.2)	180 (75.9)	86 (78.9)	77 (78.6)	163 (78.7)
Serious (grade 3)	26 (21.7)	27 (23.1)	53 (22.4)	23 (21.1)	20 (20.4)	43 (20.8)
Inflammation						
Medium (grade 1)	11 (9.2)	12 (10.3)	23 (9.7)	8 (7.3)	11 (11.2)	19 (9.2)
Moderate (grade 2)	100 (83.3)	96 (82.1)	196 (82.7)	93 (85.3)	81 (82.7)	174 (84.1)
Serious (grade 3)	9 (7.5)	9 (7.7)	18 (7.6)	8 (7.3)	6 (6.1)	14 (6.8)
Mobility limitation						
No mobility limitation (grade 0)	3 (2.5)	2 (1.7)	5 (2.1)	1 (0.9)	2 (2.0)	3 (1.4)
Medium (grade 1)	19 (15.8)	28 (23.9)	47 (19.8)	16 (14.7)	21 (21.4)	37 (17.9)
Moderate (grade 2)	94 (78.3)	83 (70.9)	177 (74.7)	88 (80.7)	72 (73.5)	160 (77.3)
Serious (grade 3)	4 (3.3)	4 (3.4)	8 (3.4)	4 (3.7)	3 (3.1)	7 (3.4)
Area of injury, n (%)						
Lower limbs	75 (62.5)	79 (67.5)	154 (65.0)	70 (64.2)	69 (70.4)	139 (67.1)
Upper limbs	44 (36.7)	38 (32.5)	82 (34.6)	39 (35.8)	29 (29.6)	68 (32.9)
Other	1 (0.8)	0	1 (0.4)	0	0	0

ITT, intention to treat; LX-P, loxoprofen patch; LX-T, loxoprofen tablet; PP, per protocol.

because of its unidimensional characteristic.[15] Therefore, the symptomatic improvement observed in our study is particularly important in complementing the findings from the primary end point. In addition, symptomatic improvements could be expected as they were also observed in the noninferiority trial assessing LX-P and LX-T for the treatment of osteoarthritis. In this trial, pain, tenderness, swelling, and inflammation, among others, were evaluated as primary outcomes, and they showed no difference between the LX-P and LX-T treatments after 2 and 4 weeks.[23]

Number needed to treat values were determined to demonstrate the clinical impact of the treatment with LX-P. The NNT has been used to evaluate the treatment effect, providing the number of patients that needs to be treated to expect an additional positive outcome (NNT) or to prevent an adverse outcome (NNTp).[8] Our analysis showed that 1 in every 14 and 15 (PP and ITT, respectively) patients have an additional response to LX-P compared with LX-T. In the literature, topical formulations of NSAIDs usually present an NNT ranging from 1 to 8.[9,10] However, these studies compared the response rate of the topical NSAID with placebo, which presents a lower frequency of responders, instead of an active comparator as in our study. In a meta-analysis of studies comparing topical and oral NSAIDs for the treatment of chronic musculoskeletal pain, the pooled results showed 55% of successful treatment in the topical NSAID group and 54% in the oral NSAID group.[9] In another meta-analysis, although there were insufficient studies for the analysis, most of the studies comparing the topical formulation with oral NSAIDs also presented a similar response rate in patients with acute musculoskeletal pain.[10] In our study, LX-P and LX-T also had a similar proportion of treatment responders, which led to a higher NNT value.

Moreover, we also evaluated the patients' perception over the treatment. After 7 days, patients from both groups reported being satisfied with the treatment: approximately 92% to 95% of patients considered the treatment extremely good or good (supplementary material, available at http://links.lww.com/PAIN/A767). Corroborating our findings, a study showed that 96% of the patients who used a topical formulation for soft tissue injury considered the treatment excellent or satisfactory.[3] In addition, 71% of these patients preferred the topical formulation instead of the oral one.[3] Another study showed that more than 50% of the patients who switched from other NSAID tape to topical loxoprofen for muscular back pain considered the latter more effective than the former.[2] These data suggest that patients may prefer topical formulations for some conditions instead of the oral one. This could be explained by the fact that LX-P not only has an analgesic effect but also is convenient because it is a once-daily patch, which may be favorable for treatment adherence.

Despite being the standard treatment, oral NSAIDs present a higher risk of adverse events, impacting patients' quality of life and possibly treatment adherence. Evidence has shown that the continuous use of oral NSAIDs is associated with increased gastrointestinal, renal, and cardiovascular toxicity.[10,11,14,22,23] The attributable risk of gastrointestinal bleeding or ulcer complication is estimated to be 2% to 4%/year among regular oral NSAID users—2 to 6 times higher than that observed in nonusers.[17,22]

Our results showed that both groups presented a low rate of adverse events, with an even lower rate in the LX-P group (14.2 and 30.8 in the LX-P and LX-T groups, respectively), and a different adverse event profile. The LX-P use resulted in a lower incidence of gastrointestinal adverse events. Several studies corroborate our safety findings, with LX-P demonstrating similar efficacy to oral drugs, but causing less adverse events, especially

Table 3

Proportion of patients who experienced treatment-emergent adverse events (TEAEs) and the total number of TEAEs.

Variable	ITT safety population	
	LX-P (n = 120)	LX-T (n = 117)
	No. of patients	No. of patients
Subjects with at least 1 TEAE, n (%)	17 (14.2)	36 (30.8)
Related TEAE, n (%)	9 (7.5)	22 (18.8)
TEAE leading to study drug discontinuation	3 (2.5)	5 (4.3)
Gastrointestinal disorders	1 (0.8)	15 (12.8)
Nausea	0	6 (5.1)
Upper abdominal pain	1 (0.8)	3 (2.6)
Diarrhea	0	2 (1.7)
Dyspepsia	0	2 (1.7)
Abdominal pain	0	1 (0.9)
Soft faeces	0	1 (0.9)
Gastritis	0	1 (0.9)
Vomiting	0	1 (0.9)
Toothache	0	1 (0.9)
Nervous system disorders	8 (6.7)	13 (11.1)
Headache	5 (4.2)	8 (6.8)
Somnolence	1 (0.8)	4 (3.4)
Dizziness	1 (0.8)	2 (1.7)
Dysgeusia	1 (0.8)	0
Administration site conditions	6 (5.0)	8 (6.8)
Application site pruritus	1 (0.8)	2 (1.7)
Application site erythema	2 (1.7)	0
Application site discomfort	1 (0.8)	0
Application site joint erythema	0	1 (0.9)
Application site pain	1 (0.8)	0
Application site reaction	0	1 (0.9)
Application site warmth	0	1 (0.9)
Renal and urinary disorders	0	2 (1.7)
Dysuria	0	1 (0.9)
Renal colic	0	1 (0.9)
Other	4 (3.3)	13 (11)

ITT, intention to treat; LX-P, loxoprofen patch; LX-T, loxoprofen tablet.

gastrointestinal ones.[2,10,14,21–23] When we considered the gastrointestinal events, the NNTp analysis showed that 1 gastrointestinal event is prevented for every 8 (ITT) patients treated with LX-P instead of LX-T. Similar results were observed in a meta-analysis that compared topical and oral NSAIDs for chronic musculoskeletal pain, showing an NNTp of 10 for gastrointestinal events.[9] For topical formulations, one of the main concerns is the high incidence of dermatological adverse events on the site of the patch application, which could impact the patients' satisfaction and adherence.[29] However, our study showed a small rate of local adverse events on both arms (5% and 6.8% in the LX-P and LX-T groups, respectively). A review also showed similar local adverse event rates in both topical NSAIDs and placebo arms.[17] This result corroborates our findings and suggests that most of the application site reactions may be associated with the vehicles and not to the drug itself.

Our study has some limitations. First, data regarding the recruitment setting (emergency or outpatient care) were not documented for each study site. Patients' characteristics could vary from one setting to another; nevertheless, it is very unlikely that this would impact study results as the selected sites are representative of the Brazilian Health Care System. Patients older than 65 years were not included in the study—an age group with high rates of NSAID use,[23] and therefore, results may be difficult to be extrapolated to this population. In addition, patients were also using concomitant medications, mostly because of comorbidities. However, both treatment groups had similar baseline characteristics. Also, the sensitivity analysis conducted to assess the impact of rescue medication use in VAS assessment was post hoc and may therefore carry statistical limitations. However, the number of patients using rescue medication was small. Finally, this study assessed the noninferiority based on the analysis of 2 active therapies. Nevertheless, the efficacy of LX-T is well established; therefore, the inclusion of a placebo arm would have been unethical, and it would not be methodologically necessary.

The study findings indicate that LX-P is effective and tolerable for the treatment of pain in patients with acute traumatic injuries, being a new option for anti-inflammatory treatment in Brazil.

Conflict of interest statement

The authors have no conflict of interest to declare.

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Appendix A. Supplemental digital content

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