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Efficacy and safety of topical NSAIDs combined with physiotherapy for frozen shoulder: a randomized controlled trial

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Abstract. – OBJECTIVE: Frozen shoulder is a prevalent condition among individuals in their middle and later years. Invasive therapy has shown promising results in the treatment of frozen shoulders, but its widespread adoption has been hampered by high costs and the need for advanced medical technology. As a result, patients with frozen shoulders often turn to non-steroidal anti-inflammatory drugs (NSAIDs) for symptomatic relief. However, the oral administration of NSAIDs can lead to troublesome adverse effects on the gastrointestinal, cardiovascular, and urinary systems. In contrast, topical NSAIDs have gained attention for their excellent efficacy and lower adverse effects in various chronic pain conditions. Therefore, our study aimed to investigate the efficacy and safety of topical NSAIDs in improving pain and mobility among patients with frozen shoulders.

PATIENTS AND METHODS: A total of 108 patients experiencing moderate to severe pain and mobility impairment due to frozen shoulder were enrolled in this study. The participants were randomly assigned to either the experimental group (n=72) or the control group (n=36). The experimental group received daily treatment with the loxoprofen hydrogel patch (LOX-P) in addition to basic rehabilitation physiotherapy. The control group was treated with flurbiprofen cataplasm (FLU-C) twice a day, along with rehabilitation physiotherapy. The primary endpoint for evaluating the efficacy of the two patches was the Constant-Murley score (CMS). Clinical symptom data, adverse events, and patient satisfaction were also recorded.

RESULTS: After 14 days of treatment, the effective rate was 66.67% (n=48) in the experimental group and 41.67% (n=15) in the control group. The overall difference in the effective rates was 25.00% (95% CI=5.20-42.52; *p*=0.013). The safety profiles of the two topical agents were similar, with only a few adverse events reported.

CONCLUSIONS: The loxoprofen hydrogel patch demonstrates a significant ability to alleviate shoulder pain and restore shoulder function in the treatment of frozen shoulder, with minimal adverse reactions.

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Key Words:
Frozen shoulder, Loxoprofen, Pain, Nonsteroidal drug.

Introduction

Frozen shoulder (FS), which is also referred to as adhesive capsulitis, fibrotic capsulitis, and contracture of the shoulder, is a very common and mysterious disease. Literature indicates that it is generally believed frozen shoulder affects approximately 2-5% of the global population, especially women approximately 50 years old[1]. People with diabetes and thyroid-related diseases, particularly hypothyroidism, have an increased risk of FS of up to nearly 40%[2]. The prevalence of frozen shoulder can be increased up to threefold in people with diabetes compared to the general population[3]. The main clinical manifestations of FS are pain, stiffness and restriction of movement[4]. The pathophysiology of FS is not clearly established. It is generally believed that FS starts as inflammation and progresses to cystic fibrosis contracture of the shoulder with synovitis[5]. In contrast to the prevailing understanding held by many in the past, studies[6,7] have found that many cases of frozen shoulder (FS) do not resolve over time, and severe cases can even lead to disability or paralysis. Therefore, early intervention and treatment are crucial to prevent the occurrence of poor prognoses. Common modalities encompass nonsurgical approaches like medical treatments, physical therapy, steroid injections, and surgical interventions such as arthroscopic capsular re-

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lease. While effective, invasive treatments come with high costs, necessitate specialized expertise, and pose potential traumatic side effects, making them less accessible and appealing[8]. Currently, the favored approach is conservative treatment due to its broad acceptance despite the lack of clear evidence supporting a single best option[8]. Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently employed in conservative treatment, playing a pivotal role in FS management.

Classic NSAIDs are known to control the development of inflammation by blocking the synthesis of human prostaglandins by effectively inhibiting cyclooxygenase. However, inhibition of cyclooxygenase not only has therapeutic effects but also often damages organs and tissues. Long-term oral NSAIDs are highly associated with cardiovascular, urinary, and especially digestive complications[9,10]. A review[11] of clinical trials on NSAIDs have strongly suggested that long-term use on NSAIDs is highly associated with digestive adverse events, such as gastritis and bleeding. In addition, nearly 50% of chronic NSAID users are found to have endoscopic lesions (such as subcutaneous bleeding, clotting, and ulcers) on examination, often without clinical presentation.

FS usually requires long-term use of NSAIDs. Topical preparations may be a useful alternative to oral preparations for patients with FS. This formulation not only provides non-inferior or greater efficacy but also significantly reduces NSAID-related adverse events compared to oral medications[12]. Currently, non-invasive treatment methods such as topical analgesics, including flurbiprofen cataplasm (FLU-C) and loxoprofen hydrogel patch (LOX-P), in combination with basic rehabilitation physiotherapy are favored by orthopedic clinics as a conventional treatment for frozen shoulder. However, the effectiveness of this approach on patients with frozen shoulder is uncertain, and there is a lack of reliable clinical studies to support its efficacy. Although FLU-C has been widely used in China for treating frozen shoulder, however, only one UK study has reported on the therapeutic effects of flurbiprofen-based topical formulations in the treatment of frozen shoulder[13]. Furthermore, this study had limited sample sizes and lacked diversity in ethnic groups. LOX-P is a new topical nonsteroidal drug widely used in many countries in East Asia. Loxoprofen is a prodrug that inhibits prostaglandin synthesis by nonselective inhibition of COX enzymes after conversion to trans-alcohol metabolites[14]. LOX-P can cause loxoprofen to penetrate directly into the affected area and relieve pain for a long time. In a clinical trial analyzed in the review by Greig et al[11], topical preparations of loxoprofen have shown promising results in improving pain and inflammatory symptoms and are well tolerated. The efficacy of loxoprofen tablets in the treatment of FS has been proven by a previous clinical study[15], while the efficacy of its topical formulation, LOX-P, has not been explored.

Current treatment management of FS varies widely among specialists, and many treatment decisions are based on personal experience rather than published evidence[16]. To offer improved treatment options for patients with frozen shoulder, it is essential to conduct more clinically efficient studies. This study aimed to explore the treatment efficacy and tolerability of LOX-P for FS in the real world.

Patients and Methods

We conducted a parallel, randomized, comparative trial (ChiCTR2100052375) using a real-world open study to investigate the treatment effect and safety of LOX-P in FS patients and compare the efficacy and safety to those of FLU-C. Subjects were recruited from the Department of Orthopedics, the Second Xiangya Hospital, where the trial was conducted. The subjects were screened and completed the follow-up study from August 2021 to January 2022. This research was conducted according to the Real-World Research Guidelines 2018 Edition, Clinical Quality Management Specifications (GCP)[17], and Chinese regulations (available at: www.nmpa.gov.cn/xxgk/fgwj/xzhgfxwj/20200426162401243.html). The study was approved by the Medical Ethics Committee of the Second Xiangya Hospital on August 21, 2021 (Clinical Study No. 109). We used CONSORT reporting guidelines to conduct the research[18].

Participants

Subjects were recruited by professional orthopedic surgeons in the orthopedics outpatient Department of the Second Xiangya Hospital. Based on the investigator's assessment, patients were considered eligible if they were between 20 and 85 years of age and had a diagnosis of FS as determined by clinical diagnostic guidelines. Patients

with shoulder pain or mobility impairment due to non-shoulder causes (e.g., vertebrae disease, rotator cuff injury, subacromial impingement injury, cholecystitis, angina pectoris, myocardial infarction) and known allergies to the study drugs (including loxoprofen and flurbiprofen) were excluded. Participation in this study was voluntary, and patients could withdraw from the experiment at any time.

Intervention

The research subjects were allocated into experimental and control groups by a completely random grouping method. The grouping was generated by the Data Science Center of the hospital where the trial was conducted, with SPSS 23.0 software (IBM Corp., Armonk, NY, USA), and the number of random seeds was 20,200,228. Treatment was initiated after confirmation of eligibility. The fundamental treatment for both groups included health education and standardized physiotherapy programs conducted under the supervision of medical professionals. The physiotherapy regimen comprised guiding patients to perform essential shoulder movements, aiming to enhance mobility and promote recovery. In the experimental group, LOX-P was administered in the pain department once a day in addition to basic treatment. The control group received FLU-C twice a day in addition to the basic treatment. LOX-P was provided by Hunan Jiudian Pharmaceutical Co., Ltd, Changsha City, Hunan Province, China. In cases where combination therapy was needed, the method of administration and treatment was consistent between the two groups. The professional head of the clinical research department designated an orthopedic surgeon to record the medication data, including the number of times medication was administered, the remaining drugs and other items, and the compliance of the subjects.

Sample Size

The number of eligible subjects was 118, of which 10 were excluded from the statistical calculation due to loss of follow-up. The final sample size was 72 in the experimental group and 36 in the control group. We analyzed and compared the two samples. There was no significant difference in demographic characteristics between the sample after the removal of the lost follow-up population and the original sample, which indicates that the lost patients did not affect the representativeness of the sample.

Endpoint

The primary endpoint was the overall response rate at week 2 based on the Constant-Murley score (CMS), which was determined with patient cooperation. After the second week of treatment, physicians and subjects calculated a joint score based on the patient's range of motion and pain at the time of follow-up. The CMS is universally adopted by the European Society of Elbow and Shoulder Surgery (ESSES). It is an effective and reliable measurement method commonly used by joint surgeons to evaluate the condition of the shoulder joint of patients. The shoulder joint was scored in eight aspects, including pain degree, influence of daily activities and range of motion. Patients were divided into four categories based on improvement in pain and activity level: cure (change from baseline ≥95%), markedly effective (change from baseline, 75% to 95%), effective (change from baseline, 30% to 75%), and ineffective (change from baseline <30%). The total effective rate of treatment refers to the proportion of the sum of cured cases, markedly effective cases and effective cases of the total cases.

The secondary criteria included visual analog scale (VAS) score, CMS, satisfaction score, and adverse reaction evaluation before treatment and 7 days and 14 days after treatment. The visual analog scale (VAS) is a very common pain assessment method that divides the scale into 10 equal parts, which are represented by 0 and 10 at the left and right ends, respectively. 0 means the patients do not feel pain, and 10 represents extreme pain. Satisfaction was assessed by the patients themselves, and there were five levels, from very satisfied to very dissatisfied. The total satisfaction was the proportion of satisfied and very satisfied patients out of the total number of patients. Safety assessment included the recording of adverse reactions, such as local irritation, redness and swelling, pruritus, tearing pain, allergy, and gastrointestinal reactions, during the study, and the results were divided into adverse events, serious adverse events, and adverse events leading to study withdrawal.

Statistical Analysis

All subjects who signed the informed consent form could choose to opt out of this clinical trial at any time. Those who failed to complete at least one dose of the trial drug and could not be evaluated for safety and efficacy were considered

dropped cases. Descriptive statistics were used to describe the graph of the sample and the clinical characteristics of the patients. Statistics Analysis System (SAS) 9.4 (SAS Institute Inc., Cary, NC, USA) software was used for data analysis. We used the mean, standard deviation, minimum, maximum, quartile and median values to describe continuous variables. Independent sample *t*-tests were used for comparisons between groups. Count data were expressed as the number of cases (rate). The *p*-value of comparisons between groups was calculated by the Chi-square test or the exact probability method, and the confidence interval of the rate difference was calculated by Newcombe-Wilson. The *p*-values of the repeated-measures data were compared using repeated-measures variance. $p<0.05$ was considered statistically significant.

Results

We stopped recruitment after sufficient subjects had been recruited in both groups. From March 2021 to January 2022, 118 patients were screened and eligible. Data from 10 patients who did not complete the assessment due to loss to follow-up were excluded, leaving 108 patients randomly allocated into the experimental and control groups (Table I). The experimental group included 72 patients, including 21 (29.17%) males and 51 (70.83%) females. Thirty-six patients were included in the control group, including 9 (25.00%) males and 27 (75.00%) females (population baseline $p=0.649$, no significant difference). The average age of the experimental group at screening was 50.24±10.90 years old, while the average age of the control group was 52.42±9.98 years old ($p=0.316$, no significant difference). A total of 78 (72.22%) women were included in the study. The demographic baseline characteristics of the LOX-P group and the FLU-C group were basically the same.

The total effective rate of the LOX-P group in the second week was 66.67% (n=48), including 3 patients in the cure group, 8 patients in the markedly effective group, and 37 patients in the effective group. The FLU-C group's effective rate was 41.67% (n=15), including 0 patients in the cure group, 1 patient in the markedly effective group, and 14 patients in the effective group. The difference in the total effective rate was 25.00% (95% CI=5.20-42.52; $p=0.013$) (Figure 1); more detailed information can be found in Table II. The total CMS was 88.85±11.62 in the LOX-P group and 83.31±12.94 in the FLU-C group, and the difference between the two groups was statistically significant ($p=0.027$). The change from baseline in the experimental group was 25.17±13.55, and the change from baseline in the control group was 17.69±9.49. The difference in baseline change between the LOX-P group and the FLU-C group was statistically significant ($p=0.004$).

The VAS scores of the LOX-P group and the FLU-C group were 6.57±1.80 mm and 6.64±1.22 mm, respectively. There were no statistically significant differences between the LOX-P group and FLU-C group at baseline ($p=0.772$). At 2 weeks after the operation, the VAS score was 2.22±1.32 mm in the experimental group and 3.00±1.22 mm in the control group ($p=0.004$). The baseline changes on day 14 were -4.35±2.22 mm in the experimental group and -3.64±1.25 mm in the control group ($p=0.079$). After 14 days of treatment, there was a statistically significant difference in the pain impression between the two groups, but there was no statistically significant difference in the

Table I. Demographic characteristics of the patients.

Parameter	LOX-P (N=79)	FLU-C (N=39)	*p*-value
Number			
N	72	36	
Gender-n (%)			0.649
Male	21 (29.17)	9 (25.00)	
Female	51 (70.83)	27 (75.00)	
Age (years)			
Mean (SD)	50.24 (10.90)	52.42 (9.98)	0.316
Median (Q1, Q3)	52.00 (41.50, 57.00)	52.50 (44.50, 58.50)	

LOX-P: loxoprofen hydrogel patch; FLU-C: flurbiprofen cataplasm; SD: standard deviation; Q1: first quartile; Q3: third quartile.

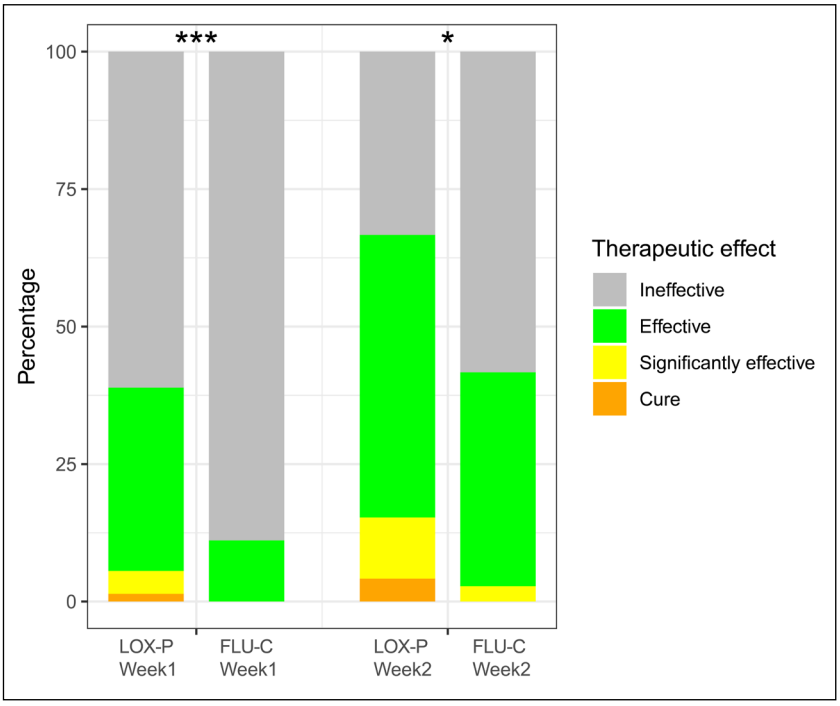

Figure 1. The percentage of treatment effects in different groups. The total effective rate of the LOX-P group, consisting of the cure rate, significantly effective rate and effective rate, is higher than that of the FLU-C group in the first and second weeks of follow-up. *p<0.05, ***p<0.005. LOX-P: loxoprofen hydrogel patch; FLU-C: flurbiprofen cataplasm.

efficacy between the experimental group and the control group. The ADL scores of the experimental group before treatment and 14 days after treatment were 9.47±2.91 and 14.36±4.33, respectively, and those of the control group were 8.78±1.81 and 11.94±3.19, respectively. The baseline change values of the experimental group and the control group were 4.89±3.77 and 3.17±2.92, respectively (p=0.018), and the difference in the efficacy change value between the two groups was statistically significant. The ROM scores of the experimental group and the control group changed from 28.65±7.84 and 31.28±8.13 to 40.53±7.62 and 38.72±8.65, respectively. The baseline changes in the LOX-P group and the FLU-C group were 11.88±7.93 and 7.44±4.84, respectively (p=0.003). The difference between the two groups was statistically significant (Table III).

Only a very low number of adverse events occurred in this study. No serious adverse events occurred. The rates of adverse events were similar in the LOX-P group and the FLU-C group (5.06% and 5.13%). Most adverse reactions were local reactions. The total satisfaction of the LOX-P group and the FLU-C group was 94.44% and 97.22% (p=0.332), respectively, and there was no statistically significant difference between the

Table II. Comparison of total effective rate between groups after treatment.

Group	N (%)				Total effective rate	p-value	Total efficiency difference of 95% confidence interval (%)
	Cure	Significantly effective	Effective	Ineffective			
Week 1							
LOX-P (N=72)	1 (1.39)	3 (4.17)	24 (33.33)	44 (61.11)	28 (38.89)	0.003	27.78 (10.16-41.13)
FLU-C (N=36)	0 (0.00)	0 (0.00)	4 (11.11)	32 (88.89)	4 (11.11)		
Week 2							
LOX-P (N=72)	3 (4.17)	8 (11.11)	37 (51.39)	24 (33.33)	48 (66.67)	0.013	25.00 (5.20-42.52)
FUL-C (N=36)	0 (0.00)	1 (2.78)	14 (38.89)	21 (58.33)	15 (41.67)		

p-values were calculated using the Chi-square test; 95% confidence intervals for the difference in total effective rates between the two groups were calculated using Newcombe-Wilson; LOX-P: loxoprofen hydrogel patch; FLU-C: flurbiprofen cataplasm; SD: standard deviation.

Table III. Comparison of indicators among treatment groups at different visits.

	Intervention			Control				
Outcome Measure	**Mean±SD**	**Change±SD**	***p*-value**	**Mean±SD**	**Change±SD**	***p*-value**	**Group *p*-value**	**Baseline *p*-value**
VAS								
Baseline	6.67±1.62	-	-	6.64±1.22	-	-	0.928	-
Week 1	3.90±1.30	-2.76±1.48	-	4.25±1.25	-2.39±0.90	-	0.188	0.166
Week 2	2.22±1.31	-4.35±2.22	<0.001	3.00±1.22	-3.64±1.25	<0.001	0.004	0.079
CMS								
Baseline	63.68±11.11	-	-	65.61±9.99	-	-	0.381	-
Week 1	79.19±11.62	15.51±10.76	-	75.58±11.62	9.97±7.68	-	0.131	0.007
Week 2	88.85±11.62	25.17±13.55	<0.001	83.31±12.94	17.69±9.49	<0.001	0.027	0.004
ADL								
Baseline	9.47±2.91	-	-	8.78±1.81	-	-	0.193	-
Week 1	12.19±3.01	2.72±2.95	-	10.78±2.76	2.00±2.29	-	0.019	0.201
Week 2	14.36±4.33	4.89±3.77	<0.001	11.94±3.19	3.17±2.92	<0.001	0.004	0.018
ROM								
Baseline	28.65±7.84	-	-	31.28±8.13	-	-	0.108	-
Week 1	35.75±8.54	7.10±5.99	-	35.22±7.96	3.94±3.96	-	0.758	0.005
Week 2	40.53±7.62	11.88±7.93	<0.001	38.72±8.65	7.44±4.84	<0.001	0.27	0.003

LOX-P: loxoprofen hydrogel patch; FLU-C: flurbiprofen cataplasm; SD: standard deviation; VAS: visual analogue scale; CMS: Constant-Murley score; ADL: activities of daily living; ROM: range of motion.

Table IV. Total satisfaction evaluation.

	N (%)					Total satisfaction	*p*-value	95% CI
Group n (%)	Very satisfied	Satisfied	Ordinary	Dissatisfied	Very dissatisfied			
LOX-P (N=72)	33 (45.83)	35 (48.61)	4 (5.56)	0 (0.00)	0 (0.00)	68 (94.44)	0.332	-2.78 (-10.98, 9.10)
FLU-C (N=36)	18 (50.00)	17 (47.22)	1 (2.78)	0 (0.00)	0 (0.00)	35 (97.22)		

Total satisfaction: very satisfied + satisfied/total number of patients; 95% CI: confidence interval for the difference in total satisfaction; LOX-P: loxoprofen hydrogel patch; FLU-C: flurbiprofen cataplasm.

two groups (Table IV).

Discussion

Numerous people in their 40s and 50s experience shoulder stiffness, difficulty moving, and severe pain, known as FS. Similar symptoms and pathological changes can be seen in other joints, such as the wrist, hip and ankle[19-21]. Experts have been exploring the therapeutic management of FS, and increasingly effective treatments are beginning to emerge. However, medication therapy remains the most common option for patients. Medication therapy is effective and convenient for controlling the inflammation that drives the development of FS. NSAIDs are widely used by FS patients for pain relief and functional improvement. However, the associated side effects caused by the long-term use of conventional oral NSAIDs have also troubled patients and physicians.

NSAIDs significantly relieve acute and chronic pain in patients by controlling the development of inflammation and reducing the production of prostaglandins. However, side effects caused by the absorption of traditional oral NSAIDs in the gastrointestinal tract have led to the exploration of the feasibility of topical applications in the hope of achieving superior therapeutic results while avoiding the associated side effects. Recent studies[22-25] of other NSAIDs for acute and chronic pain have shown that topical NSAIDs outperform oral NSAIDs. Local preparation can maintain low blood concentrations and achieve high local tissue concentrations, significantly reducing systemic exposure while maintaining local efficacy and reducing the occurrence of adverse reactions[26]. Topical agents have become a better option for patients who require long-term use of NSAIDs[22]. While many patients are starting to opt for topical NSAIDs for frozen shoulder, we have found no reliable evidence of associated efficacy. Therefore, we would like to explore the clinical efficacy and safety of currently commonly used nonsteroidal topical preparations in the treatment of FS. Loxoprofen is a new topical nonsteroidal drug. As a prodrug, loxoprofen produces its effects through carbonyl reductase metabolism in local tissues (the skin and liver) to form the active metabolite in the trans-OH form, and its efficacy is further enhanced by the extremely high carbonyl reductase levels in the skin[23]. Loxoprofen is well suited for use as a topical preparation. LOX-P is used in East Asian countries such as China and Japan to treat chronic pain from numerous diseases. Topical loxoprofen has shown excellent performance in the treatment of diseases such as osteoarthritis, myalgia, and traumatic pain[22,24,27]. Notably, for diabetic patients who are prone to FS, scholars have found[28] that topical loxoprofen can effectively reduce pain without significantly affecting renal function and blood pressure. We selected FLU-C, the most common topical NSAID formulation in the Chinese market, as a control drug. Flurbiprofen is an NSAID with the strongest analgesic and anti-inflammatory effects among propionates. It is 250 times more anti-inflammatory and 50 times more analgesic than aspirin.

This study constitutes a real-world prospective investigation aimed at assessing the effectiveness and tolerability of frequently employed topical NSAIDs for FS. Given the real-world prevalence of frozen shoulder, the study primarily enrolled female subjects. The participant pool included individuals with concomitant conditions such as diabetes, thyroid-related diseases, and hypertension. This study underscored the comprehensive treatment approach for frozen shoulder, encompassing health education, exercise, and physician-guided physical therapy, along with the use of topical non-steroidal drugs.

A substantial proportion of patients in our trial had severe acute shoulder pain and mobility impairment at baseline. After treatment, the results show that LOX-P shows great tolerability in the treatment of FS and can effectively alleviate pain and improve functional problems. Efficacy was evident in most patients, as indicated by the scores after two weeks of treatment compared to baseline. A total of 66.67% of patients improved by more than 30% within 2 weeks, and 4.17% of patients improved by more than 95% within 2 weeks. This result sufficiently demonstrates the efficacy of LOX-P in FS treatment. Compared with the control drug (FLU-C), the total efficacy rate of LOX-P was 25% higher after 2 weeks. The difference in treatment effects shown in this study is striking. The secondary endpoints of VAS pain score, ROM score for mobility, and ADL score for life functioning were more informative. Both LOX-P and FLU-C showed excellent analgesic effects on VAS pain scores, with improvements from baseline of approximately 65% and 55%, respectively.

LOX-P was not significantly superior to FLU-C in relieving pain caused by a frozen shoulder. However, the ADL score and ROM score showed that LOX-P was significantly better than FLU-C in improving quality of life and functional activities. ROM and ADL assessed subjects' shoulder internal rotation, abduction, and hand elevation abilities. These two items are more objective evaluation indicators, and the results have high credibility. The active metabolic form of loxoprofen,

loxoprofen-SRS (an active metabolite of loxoprofen sodium), improved inflammatory edema in a concentration-dependent manner[29]. The skin has an extremely high carbonyl reductase level, which can significantly increase the concentration of loxoprofen-SRS. We speculate that this may account for the apparent functional improvement.

No serious adverse events occurred during treatment with either topical formulation. The rates of digestive damage often associated with NSAIDs and skin reactions associated with topical formulations were lower. Only 5.56% of the patients in the LOX-P group experienced local skin-related adverse events. Relevant literature[30] has shown that loxoprofen lacks a benzophenone chromophore, an important chemical structure that causes photosensitive dermatitis, which may be the reason for minor skin reactions. While no evident gastrointestinal disorders occurred, this may be attributed to the low concentration of the skin topical preparation in the blood[25]. The safety advantage of topical loxoprofen has also been demonstrated in studies[11] treating osteoarthritis, myalgia, and traumatic pain. Our study further complements the safety of topical NSAID use in FS in real-world clinical practice. Finally, we also conducted a satisfaction survey of the subjects. Total satisfaction was approximately 95% in both groups. LOX-P has high water content, excellent air permeability, slight irritation, and other advantages, which indeed give patients an excellent experience and leave a favorable impression. However, some patients reported that the preparation was somewhat chilly when used in winter. Non-hydrogel patches may be an alternative for winter.

This article has the following limitations: the population of this study is Chinese of relatively single origin, and other ethnic groups need to be explored. The sample size was relatively small, and we did not further investigate the differences in treatment effects between different periods of pain, different age groups, and different comorbidities.

Conclusions

The loxoprofen hydrogel patch can significantly relieve pain and restore shoulder function in patients with frozen shoulders with few side effects.

Conflict of Interest

The authors declare that the research was conducted without any commercial or financial relationships that could potentially create a conflict of interest.

Ethics Approval

The study was approved by the Medical Ethics Committee of the Second Xiangya Hospital on August 21, 2021 (Clinical Study No. 109). This study is registered with the Chinese Clinical Trial Registry (ChiCTR2100052375).

Informed Consent

Each subject signed a written informed consent.

Availability of Data and Materials

The original contributions presented in the study are included in the article material; further inquiries can be directed to the corresponding author.

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Authors' Contribution

Conceptualization, Hui Li, Xinzhan Mao; methodology: Guanyi Chen, Hui Li, XinZhan Mao; formal analysis: Guanyi Chen, Chuqiao Zhou; data curation: Guanyi Chen, Chuqiao Zhou, Hui Li, Xinzhan Mao; writing-original draft preparation: Guanyi Chen, Chuqiao Zhou; writing-review and editing: Guanyi Chen, Chuqiao Zhou; supervision: Hui Li, Xinzhan Mao; project administration: Hui Li, Xinzhan Mao. All authors have read and agreed to the published version of the manuscript.

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