Improvement of Pain and Function After Use of a Topical Pain Relieving Patch: Results of the RELIEF Study

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ORIGINAL RESEARCH

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Purpose: Pain is the most common reason for patients to consult primary care providers. Identification of effective treatments with minimal adverse events is critical to safer opioid-sparing and multi-modal approaches to pain treatment. Topical analgesic patches target medication to peripheral sites of pain while potentially avoiding adverse effects associated with systemic medications. Opioids, prescription nonsteroidal anti-inflammatory drugs, and over-the-counter oral medications are associated with systemic toxicities, increasing morbidity and mortality. This study evaluated a topical analgesic pain-relieving patch in reducing pain severity and improving function in patients with mild to moderate arthritic, neurological, or musculoskeletal pain.

Patients and Methods: This Institutional Review Board-approved study evaluated the effectiveness of a topical pain-relieving patch in reducing Brief Pain Inventory (BPI) scores in patients. The treatment group (TG) (n=152) received patches for 14 days. A control group (CG) (n=47) did not receive the patch. After day 14, 34 CG patients crossed over to treatment (CROSSG) with the patch. Surveys were administered to patients at baseline and 14 days to assess changes in pain severity and interference. Changes in oral pain medication use, side effects, and satisfaction use were also assessed.

Results: Paired data were collected in the CG, TG and CROSSG. At day 14, TG pain severity score and pain interference score decreased (49% and 58.1%, respectively). Pain severity and interference scores decreased less in the CG (12.3% and 14.8%, respectively). In the study, 60.5% of the TG were using concomitant oral pain medications "a lot less", and 90.8% were very/extremely satisfied with the patch. CROSSG patients showed similar reductions in pain severity and interference scores after patch treatment. No side effects of treatment were reported.

Conclusion: Results indicate that this topical analgesic pain-relieving patch can reduce BPI pain severity and interference scores in adult patients with mild to moderate arthritic, neurological, and musculoskeletal pain and should be considered as a treatment option.

Keywords: methyl salicylate, menthol, analgesic, Salonpas

Introduction

Pain is the most common reason for patients to consult primary care providers.[1,14] Evaluation of effective treatments for pain relief is critical to identify safer opioid-sparing approaches to pain treatment. Chronic pain is often treated by oral opioids, yet data[15] suggest that patients still do not achieve adequate pain relief. Opioid based, nonsteroidal anti-inflammatory drugs, and common, over-the-counter oral medications have been associated with end-organ dysfunction including

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gastrointestinal (GI), cardiovascular (CV), renal and hepatic events.[16,21] Alternative pain relief options have become increasingly common and include a combination of pharmacotherapy and non-pharmacological interventions.

Successful pain treatments, including multi-modal strategies, can address negative effects associated with chronic pain conditions, including a patient's quality-of-life,[6,7,22,25] psychological well-being, and their everyday functional abilities.[14,26,27]

National initiatives that include new guidelines and strategies have recently been published highlighting safe and effective pain management options. One group of therapies that have been suggested as a first-line treatment option are topical analgesics, a targeted therapy aimed at the location of pain. Previous research supports that topical agents are effective and safe for patients with chronic pain.[17,21] By targeting the nociceptor pathways,[28] topical formulations have reduced risk of systemic adverse events because of significantly less plasma exposure, bypassing absorption in the gastrointestinal (GI) track, while delivering effective concentrations in the targeted tissues.[29,30] Limited drug–drug interactions, less potential for misuse, ease of application, direct application to the targeted site of pain, patient satisfaction, and success in treating the patient's pain can provide advantages over systemically delivered oral medications.[17,21,31,35]

Although adverse GI and renal side effects appear reduced with topical versus oral diclofenac, the US Food and Drug Administration (FDA) mandates that warnings be placed on all NSAID products about the risks of GI and CV adverse effects.

This Relieving Pain: Evaluating Patient Quality of Life Improvement – Perceptions, Experience and Feedback After Use of A Topical Pain Relief Patch (RELIEF) study evaluated patients with mild to moderate and acute and chronic pain conditions and their overall perceptions of pain treatment and associated symptoms with the use of a specific topical pain-relieving patch (Salonpas® Pain Relieving Patch. Hisamitsu Pharmaceutical Company, Inc, Japan). This formulation is an over-the-counter (OTC) analgesic topical pain patch that includes menthol, camphor, and methyl salicylate as the active ingredients. Menthol and camphor are topical analgesics which provide analgesia by activating and then desensitizing epidermal nociceptors[29,36] including transient receptor potential vanilloid subtype 1 (TRPV1) channels.[37] Methyl salicylate has been associated with significant pain relief with minimal adverse events[38] and is hydrolyzed to salicylic acid, in

the skin and surrounding tissue, providing local anti-inflammatory effects, inhibiting the Cox-1 and Cox-2 enzyme receptor pathways of the Arachidonic Acid cascade increasing the threshold for nerve firing and pain.[39]

This study assessed changes in Brief Pain Inventory short form (BPI) pain severity scores and pain interference scores, as well as a change in the use of pain medications other than the patch within and between control, treatment, and crossover groups.

Methods
Study Design
This study was a prospective, Institutional Review Board-approved Observational Study used to evaluate patients treated with an OTC topical pain-relieving patch containing methyl salicylate 10%, menthol 6%, and camphor 3.1%. Following informed consent, patients who met the eligibility criteria and who were treated with the pain-relieving patch comprised the study's test groups (treatment group—TG, and control to treatment group–CROSSG), and patients who met the eligibility criteria but were not treated with the pain-relieving patch comprised the study's control group (CG). Patient answers to the baseline and day 14 surveys were used to evaluate pain relief by comparing answers to validated pain measurement scales (eg, BPI) as well as other survey questions that consider patient satisfaction.

This study was performed in full accordance with the rules of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and the principles of the declaration of Helsinki and the international council of Harmonisation/GCP. The study protocol was approved by IntegReview institutional review board.

Patients
Clinicians at five United States (US) investigator sites invited patients who were eligible to enroll in the study. For the treatment groups, inclusion criteria were as follows: 1) ages 18 to 64 years, inclusive; 2) ability to provide written informed consent; 3) received a topical pain-relieving patch from their treating physician; 4) had been diagnosed with a mild to moderate pain condition. Patients who were a beneficiary of a government-funded healthcare program, patients who currently or who have had a history of use of illicit or prescription drugs of abuse, and patients who were pregnant were ineligible to participate in the study. A CG of patients who met

inclusion criteria but did not receive the medication were also enrolled and subsequently evaluated alongside the TG patients. A sub-group of CG patients who were observed for 14 days while not being treated with the pain-relieving patch crossed over to the TG (CROSSG) and were observed for another 14 days while on treatment.

Each site provided patients an identification number to keep personal information confidential in compliance with the HIPAA, and a confidential file containing the informed consent forms and patient identification numbers were kept and maintained in a secured cabinet only accessible to the principal investigator and authorized personnel. Patient survey responses were provided to Clarity Science with no identifying information about patients.

Patients could withdraw from this study at any time with the assurance of no harmful or unfavorable impact on their medical care. All diagnostic tests and treatment decisions were made at the discretion of physicians, with no tests, treatments, or investigations performed as part of this study.

Topical Intervention

The study aimed to evaluate patients who had been prescribed an OTC topical pain-relieving patch, the Salonpas® Pain Relieving Patch (Hisamitsu Pharmaceutical Company, Inc, Japan) containing methyl salicylate 10%, menthol 6%, and camphor 3.1% from their physician or clinician. Patient consent and compliance, as well as treatment outcomes, were collected for the duration of the study. Study subjects were instructed to apply the patch every 8 hours, except during overnight hours for 14 days.

Study Procedures and Assessments

At the time of enrollment, patients were asked to complete a baseline survey and were then asked to complete follow-up surveys on days 3, 7, and 14 of the study period. Baseline to day 14 results are reported here.

The baseline and follow-up surveys are comprised of questions to address the primary pain complaint of the patient. The primary pain complaint was indicated as the follows: 1) arthritis; 2) neuropathy or radiculopathy; 3) myofascial or musculoskeletal pain or spasm; or 4) other. Once patients chose their primary pain complaint, and confirmed by the clinician, they indicated the location of that pain in areas such as hands, feet, hips, knees, neck, shoulders, and back, among others. Patients indicated only one pain complaint and location of pain for which the medication was primarily being used.

Patients completed the BPI as part of each survey. The BPI is often used as a measure of pain for a wide range of

conditions including cancer, musculoskeletal disorders, depressive conditions, and surgical pain. The BPI is commonly recommended for use in clinical trials of patients with acute and chronic pain conditions[26,40] and has adequate internal consistency, acceptable-to-excellent test–retest reliability, satisfactory-to-good construct validity, criterion validity, and is sensitive to change.[41,44] Ratings on the BPI are based on a 0–10 numerical scale. For the questions about pain severity, 0 is "no pain" and 10 is "pain as bad as you can imagine." For the questions about pain interference with activities of daily living, 0 is "does not interfere" and 10 is "completely interferes." Patient responses to questions regarding pain severity and pain interference were compiled to yield the overall score for pain severity and pain interference.

Patients were asked to indicate any other medications that they had been taking for pain relief at the time of the baseline and the day 14 survey. Categories of medications that patients could choose included OTC agents (eg, ibuprofen, naproxen, acetaminophen, acetylsalicylic acid, and other pain medications such as creams, gels, roll-ons, sprays, patches or rubs), prescription NSAIDs (eg, naproxen sodium, celecoxib, meloxicam or diclofenac), prescription opioids (eg, fentanyl, hydrocodone, hydromorphone, morphine or oxycodone), or prescription anticonvulsants (eg, gabapentin or pregabalin). Patients could indicate more than one type of pain relief medication in each of the four categories of pain medication.

Study End Points

There were five primary endpoints:

1. Changes from baseline to day 14 in BPI mean pain severity and interference scores within the CG, TG and CROSSG for the primary pain complaint.
2. Differences in changes from baseline to day 14 in BPI mean pain severity and interference scores between the CG, TG and CROSSG for the primary pain complaint.
3. Changes from baseline to day 14 in the use of prescription and OTC medications (other than the OTC pain relieving patch) within the CG and TG.
4. Patient satisfaction with the topical pain-relieving patch treatment.
5. Any side effects reported by patients.

Statistical Analysis

For all variables, descriptive statistics were calculated, including frequencies and percent for categorical variables

and means with standard deviation (SD) for continuous variables. The maximum sample size available was used for each statistical analysis.

Changes from baseline to day 14 in BPI mean pain severity and pain interference scores were analyzed using the paired t-test to identify any statistically significant differences within each of the CG, TG and CROSSG. The unpaired t-test was used to identify any statistically significant differences in the amount of change in BPI mean pain severity and pain interference scores from baseline to day 14 between the CG, TG and CROSSG.

Each survey collected the numbers and types of prescription and OTC oral/topical medications being used for pain relief; statistically significant differences in the use of these types of medications from baseline to day 14 were determined using the McNemar test and χ^2 test for binomial paired and unpaired data, respectively. Descriptive statistics were used to determine patient satisfaction with the pain-relieving patch within those treated. Descriptive statistics were also used to report any side effects experienced by patients.

A two-tailed alpha was set to 0.05 for all statistical comparisons. SPSS v. 23 was used for all analyses.

Results
Baseline Demographic and Clinical Characteristics of Patients

A total of 199 patients at 5 US investigator sites were enrolled in the study and completed the baseline and day 14 surveys. The total number of patients in the TG receiving the pain-relieving patch was 152, and the total number of patients in the CG who did not receive the pain-relieving patch was 47. The total number of patients in the CROSSG was 34.

Demographic results were similar for gender and age at the baseline survey for the CG, TG, and CROSSG (Table 1). Of the 47 patients in the CG, 20 (42.6%) were male and 27 (57.4%) were female. The 152 patients in the TG had a total of 52 (34.2%) male and 100 (65.8%) female patients. The mean age was 48.4 years for the CG and 45.4 years for the TG. For the 34 patients in the CROSSG, 14 (41.2%) were male and 20 (58.8%) were female. Mean age at baseline was 47.3 years for this crossover group. The number of females in the TG is not statistically significantly different from the number of females in the CG or the CROSSG (P = 0.303 and 0.437, respectively, Fisher's Exact Test).

The primary pain complaint for the CG, TG, and CROSSG patients was recorded at baseline (Table 1).

Table 1 Baseline Demographic and Clinical Characteristics of the Control, Treatment and Crossover Groups

Variable	Control Group	Treatment Group	Crossover Group
Number of patients	47	152	34
Age (years)			
Mean (SD)	48.4 (10.5)	45.4 (11.8)	47.3 (11.0)
Median	47.8	46.5	46.9
Min, max	23.4, 64.8	18.1, 64.6	23.4, 62.6
Sex, n (%)			
Female	27, (57.4)	100 (65.8)	20 (58.8)
Male	20, (42.6)	52 (34.2)	14 (41.2)
Primary pain complaint, n (%)			
Arthritis	9 (19.1)	38 (25.0)	3 (8.8)
Neuropathy/radiculopathy	5 (10.6)	15 (9.9)	4 (11.8)
Myofascial/musculoskeletal	33 (70.2)	93 (61.2)	27 (79.4)
Other	—	6 (3.9)	—
Months with primary pain complaint, n (%)			
<1	5 (10.6)	3 (2.0)	5 (14.7)
1–3	4 (8.5)	29 (19.2)	4 (11.8)
3–12	17 (36.2)	49 (32.5)	6 (17.6)
>12	21 (44.7)	70 (46.4)	19 (55.9)
Hours with pain each of last 3 days			
Mean (SD)	13.4 (6.6)	8.7 (5.5)	15.1 (7.1)
Median	10.0	8.0	15
Min, max	6, 24	1, 24	6, 24
Patients taking concurrent pain medication/s, n (%)			
None	—	10 (6.6)	—
OTC	22 (46.8)	92 (60.5)	22 (64.7)
Prescription NSAID	12 (25.5)	56 (36.8)	12 (35.3)
Opioid or anticonvulsant	7 (14.9)	5 (3.3)	7 (20.6)
Muscle relaxant	4 (8.5)	5 (3.3)	4 (11.8)

Abbreviations: SD, standard deviation; Min, minimum; Max, maximum; OTC, over-the-counter; NSAID, nonsteroidal anti-inflammatory drug.

Myofascial/musculoskeletal pain was the most prominent pain complaint indicated by 70.2% (n=33) patients in the CG, 61.2% (n=93) in the TG and 79.4% (n=27) in the CROSSG patients. Arthritis was the next most common pain complaint for 19.1% (n=9) CG patients and 25.0% (n=38) of patients in the TG. Just 10.6% (n=5) of the CG patients and 9.9% (n=15) of the TG patients indicated that neuropathy/radiculopathy was their primary pain complaint. Only 3.9% (n=6) of the TG patients listed "other" as their primary pain complaint. For the CROSSG, 11.8% (n=4) had a primary neuropathy or radiculopathy complaint and 8.8% (n=3) an arthritis complaint, with no other complaints noted.

Table 2 Baseline and Day 14 Brief Pain Inventory Scores for Overall Severity, Severity Questions, Overall Interference, and Interference Questions for the Control, Treatment, and Crossover Groups

Variable	Baseline			Day 14		
	CG	TG	CROSSG	CG	TG	CROSSG
Number of patients	47	152	34	47	152	34
Overall pain severity						
Mean (SD)	5.7 (2.1)	4.9 (1.5)	5.4 (1.9)	5.0 (1.7)	2.5 (1.5)	2.8 (1.4)
Median	5.8	4.8	5.8	5.0	2.3	2.8
Min, max	2.3, 10.0	1.0, 9.3	1.5, 10.0	1.5, 10.0	0.0, 6.5	0.8, 5.8
Worst pain in last 24 hours						
Mean (SD)	7.7 (1.7)	7.2 (1.8)	7.0 (1.9)	6.6 (1.8)	4.4 (2.1) 4.0	4.0 (1.6)
Median	8.0	7.0	7.0	6.0	0, 10	4.0
Min, max	5, 10	1, 10	3, 10	3, 10		1, 7
Least pain in last 24 hours						
Mean (SD)	3.9 (2.0)	3.1 (1.8)	3.6 (2.0)	3.6 (1.7)	1.3 (1.2)	1.6 (1.1)
Median	4.0	3.0	3.0	3.0	1.0	1.0
Min, max	0, 10	0, 10	0, 10	0, 10	0, 5	0, 4
Average pain						
Mean (SD)	5.6 (2.6)	4.7 (1.6)	5.3 (2.2)	4.8 (2.1)	2.5 (1.8)	2.8 (1.4)
Median	5.0	5.0	6.0	5.0	3.0	3.0
Min, max	1, 10	1, 10	1, 10	1, 10	0, 7	1, 6
Current pain						
Mean (SD)	5.6 (2.8)	4.5 (2.0)	5.5 (2.2)	5.0 (2.1)	1.9 (1.7)	2.8 (1.6)
Median	6.0	4.5	6.0	5.0	1.0	3.0
Min, max	1, 10	0, 10	1, 10	1, 10	0, 7	0, 6
Overall pain interference						
Mean (SD)	5.4 (2.8)	4.3 (1.8)	5.5 (2.4)	4.6 (2.5)	1.8 (1.6)	2.5 (1.7)
Median	5.9	4.0	6.1	5.1	1.3	2.7
Min, max	1.6, 10.0	0.7, 9.7	1.6, 9.0	1.6, 9.0	0.0, 8.0	0.1, 5.7
Pain interference with general activity						
Mean (SD)	7.4 (1.9)	6.0 (2.2)	7.2 (1.8)	6.8 (1.8)	3.0 (2.1)	4.1 (2.0)
Median	7.0	6.0	7.5	6.0	3.0	4.5
Min, max	4, 10	0, 10	4, 10	4, 10	0, 10	1, 8
Pain interference with mood						
Mean (SD)	4.5 (3.9)	3.4 (2.9)	5.0 (3.5)	3.7 (3.6)	1.4 (2.1)	1.7 (1.4)
Median	4.0	3.0	6.0	4.0	0.0	2.0
Min, max	0, 10	0, 10	0, 10	0, 10	0, 10	0, 5
Pain interference with ability to walk						
Mean (SD)	6.6 (2.3)	5.3 (2.6)	6.2 (1.9)	5.7 (1.8)	2.1 (1.9)	2.7 (1.9)
Median	6.0	6.0	6.0	5.0	2.0	3.0
Min, max	3, 10	0, 10	3, 9	3, 9	0, 8	0, 7
Pain interference with normal work						
Mean (SD)	6.7 (2.2) 7.0	5.6 (2.3)	6.3 (1.8)	5.7 (1.8)	2.2 (1.9)	2.7 (2.0)
Median	3, 10	6.0	6.0	6.0	2.0	3.0
Min, max		0, 10	3, 9	3, 9	0, 10	0, 7

(*Continued*)

Table 2 (Continued).

Variable	Baseline			Day 14		
	CG	TG	CROSSG	CG	TG	CROSSG
Pain interference with social relationships						
Mean (SD)	3.3 (3.6)	2.1 (2.5)	3.8 (3.0)	2.8 (3.1)	0.8 (1.6)	1.6 (1.4)
Median	2.0	1.0	4.0	0.0	0.0	2.0
Min, max	0, 10	0, 10	0, 9	0, 9	0, 9	0, 4
Pain interference with sleep						
Mean (SD)	4.5 (4.5)	3.6 (3.1)	5.0 (3.5)	3.6 (3.8)	1.5 (2.0) 0.0	2.5 (2.0)
Median	3.0	3.0	6.5	3.0	0, 8	3.0
Min, max	0, 10	0, 10	0, 9	0, 9		0, 6
Pain interference with life enjoyment						
Mean (SD)	4.7 (3.0)	4.3 (2.4)		3.6 (3.0)	1.3 (1.8)	2.3 (1.9)
Median	4.0	4.0		3.0	1.0	2.0
Min, max	1, 10	0, 10		0, 10	0, 10	0, 6

Abbreviations: CG, control group; TG, treatment group; CROSSG, crossover group; SD, standard deviation; Min, minimum; Max, maximum.

At baseline, CG study participants who indicated myofascial/musculoskeletal pain as their primary complaint noted that their back was the most common location of pain (n=15). In the TG, the most commonly noted musculoskeletal pain complaint location included back and lower extremities (n=72 patients).

The length of time patients had the primary pain complaint was similar for all three groups. The greatest proportion within each group had the pain for more than 1 year: CG=44.7%, TG=46.4%, and CROSSG=55.9%, indicating a chronic pain condition. Mean amount of time in hours of pain per day for the last 3 days were: CG=13.4 (SD=6.6), TG=8.7 (SD=5.5), and CROSSG=15.1 (SD=7.1).

Baseline BPI Severity and Interference Scores

The mean BPI pain severity score at baseline was higher for the CG (5.7) compared to the TG (4.9), 95% CI: 0.2, 1.5 (Table 2). The baseline mean BPI interference score was also higher for the CG (5.4) compared to the TG (4.3), 95% CI: 0.2, 1.9. In the CROSSG, the severity and interference scores were 5.4 and 5.5, respectively, at the beginning of the treatment period—similar to the CG scores.

BPI Pain Severity Scores
Changes from Baseline to Day 14 Within and Between the CG, TG and CROSSG

The TG showed a 49.0% decrease (4.9 to 2.5, 95% CI: 2.1, 2.6) and the CG showed a 12.3% decrease in mean BPI pain severity scores from baseline to day 14 (5.7 to

5.0, 95% CI: 0.4, 1.0), see Figure 1A. The mean pain severity score decrease was significantly greater in the TG as compared to the control group (95% CI: 1.3, 2.0), see Figure 2A. The CROSSG reported a 15.6% decrease in BPI pain severity score from baseline to day 14 before receiving treatment (6.4 to 5.4, 95% CI: 0.8, 1.2); after crossing over, a 48.1% decrease in mean BPI pain severity score was noted from treatment baseline to treatment day 14 (5.4 to 2.8, 95% CI: 0.8, 1.2). The mean pain severity score decrease in the CROSSG was significantly greater during their treatment period as compared to their control period (95% CI: 1.1, 2.0).

For each of the questions which comprise the BPI pain severity score (pain at its worst and least in the last 24 hours, pain right now, and how much pain on average), see Table 2, changes in mean scores from baseline to day 14 decreased statistically significantly for both the CG and the TG, except for pain at its least in the CG. The amount of decrease from baseline to day 14 was greater for the TG compared to the CG for each of these questions.

BPI Pain Interference Scores
Changes from Baseline to Day 14 Within and Between the CG, TG and CROSSG

BPI pain interference scores (which include quality of life (QoL) parameters and ratings of: general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life) decreased statistically significantly from baseline to day 14 for both the CG and TG (Figure 1B). The TG had a 58.1% decrease from 4.3 to 1.8,
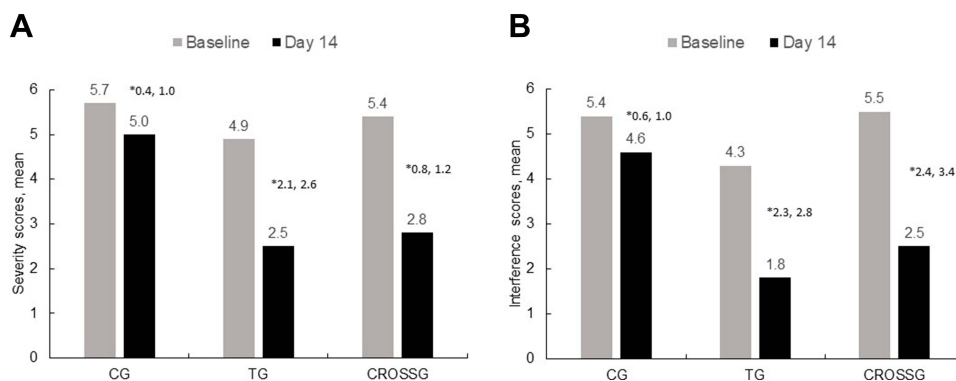
A

B

Figure 1 Baseline and day 14 overall mean (**A**) severity and (**B**) interference scores within the control, treatment, and crossover groups. *95% Confidence Interval of the difference, paired *t*-test. Each difference is statistically significant.
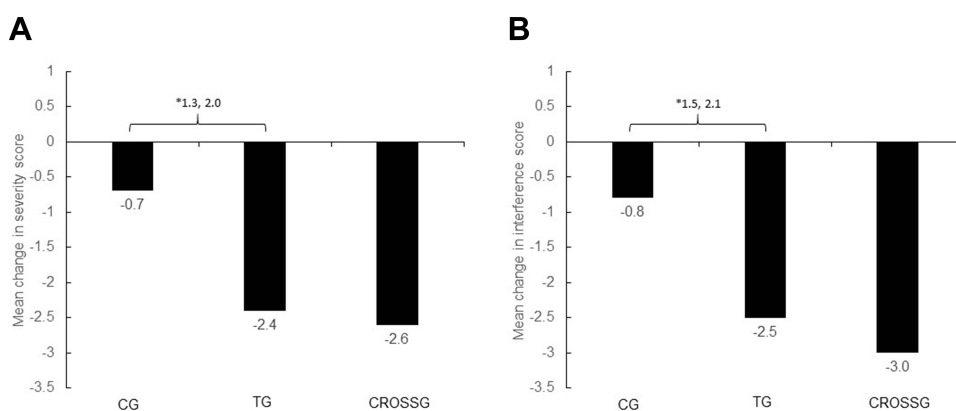**Abbreviations:** CG, control group; TG, treatment group; CROSSG, crossover group.

A

B

Figure 2 Mean change from baseline to day 14 in overall severity (**A**) and interference (**B**) scores within the control, treatment, and crossover groups. *95% Confidence Interval of the difference, unpaired *t*-test.
Abbreviations: CG, control group; TG, treatment group; CROSSG, crossover group.

95% CI: 2.3, 2.8, and the CG had a 14.8% decrease in mean BPI interference score from 5.4 to 4.6, 95% CI: 0.6, 1.0. The amount of decrease in mean pain interference scores from baseline to day 14 was statistically significantly greater for the TG compared to the CG (95% CI: 1.5, 2.1), see Figure 2B. The CROSSG reported a 14.1% decrease in mean BPI pain interference score from baseline to day 14 before receiving treatment (6.4 to 5.5, 95% CI: 0.7, 1.2). After crossing over to treatment, these 34 patients reported a 54.5% decrease in mean BPI pain interference score from treatment baseline to treatment day 14 (5.5 to 2.5, 95% CI: 2.4, 3.4). The mean pain interference score decrease in the CROSSG was significantly greater during their treatment period as compared to their control period (95% CI: 1.4, 2.5).

For each of the questions which comprise the BPI pain interference score, changes in mean scores from baseline to day 14 decreased statistically significantly for both the CG and the TG. The amount of decrease from baseline

to day 14 was statistically significantly greater for the TG compared to the CG for each of these questions.

Changes in Self-Perceived Pain Relief from Medications

One of the BPI questions (not part of the pain severity or interference scores) asks the patient how much pain relief (from 0%=no relief to 100%=complete relief in increments of 10%) they have experienced from treatments or medications within the last 24 hours. In the TG, the 87.5% increase in relief was statistically significant (39.9% at baseline to 74.8% at day 14, 95% CI: −39.9, −29.9). In the CG, the 12.0% increase in relief was not statistically significant (26.6% relief at baseline to 29.8% at day 14, 95% CI: −6.81, 0.44). The amount of change in percent relief from baseline to day 14 was statistically significantly greater for the TG compared to the CG (95% CI: −37.8, −25.6).
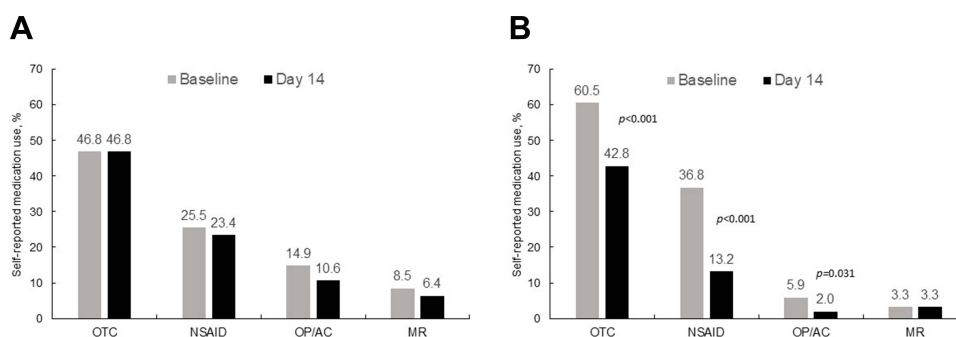
Figure 3 Percent using each type of pain medication at baseline and day 14 within the control (**A**), and treatment (**B**) groups.
Abbreviations: OTC, over-the-counter; NSAID, nonsteroidal anti-inflammatory drug; OP, opioid; AC, anticonvulsant; MR, muscle relaxant.

Concurrent Pain Medications

Changes from Baseline to Day 14 Within the CG and TG

In each survey, patients indicated the type of medication they were taking for pain relief including OTC pain medications, prescription anti-inflammatory medications, opioids or anticonvulsants, or muscle relaxants. In the CG there were 34 patients (72.3%) taking at least one medication at baseline with no reported change in the number of patients taking at least one medication at day 14. At baseline in the TG, there were 142 (93.4%) patients taking at least one medication. At day 14, that number had decreased by 37.3% to 89 (58.6%) patients taking at least one medication (P<0.001, McNemar test).

The total number of patients taking OTC pain medication at baseline in the CG was 22 (46.8%) while in the TG it was 92 (60.5%). There was no change in OTC pain medication within the CG; the 22 patients who reported use at baseline also reported use at day 14 (see Figure 3A). OTC pain medication use decreased by 29.3% in the TG, decreasing from 92 patients (60.5%) to 65 patients (42.8%), see Figure 3B. Ibuprofen was the highest reported OTC pain medication in use at baseline (38.3% in the CG and 41.4% in the TG). Acetaminophen was the second most common OTC pain medication used by 19.1% of the CG and 17.1% of the TG. As far as prescription anti-inflammatory medication, diclofenac (CG=19.1%, TG=19.1%) was reported most often. When evaluating changes in ibuprofen, acetaminophen, and Voltaren at day 14 of the TG, there was a reduction in these adjuvant analgesics of between 24%, 39%, and 62%, respectively.

Naproxen was the next highest reported prescription (CG=2.1%, TG=7.9%). The total number of patients taking prescription anti-inflammatory medication at baseline in the CG was 12 (25.5%), with an 8.3% decrease at day 14 to 11 patients (23.4%). The TG reported 56 patients (36.8%) taking these prescription pain medications at baseline and showed a 64.3% decrease in use to 20 patients (13.2%) by day 14. Use of diclofenac in the CG remained the same (19.1%) from baseline to day 14, while TG use decreased from 19.1% to 9.2%.

Although a minority of patients reported using opioids, anticonvulsants, and muscle relaxants, there was a clear trend in the treatment group toward a decrease in these agents as compared to baseline.

Separate from indicating use of specific medications for pain, patients in the TG and CROSSG were asked how their use of oral pain medications had changed (scale: 1=A lot more, 2=More, 3=No change, 4=Less, 5=A lot less). At day 14 the mean rating was 4.5 (SD=0.7, n=151) for the TG with 88.8% reporting "less" or "a lot less." For the CROSSG at treatment day 14, the mean rating was 4.4 (SD=0.5, n=34) with 100% reporting "less" or "a lot less."

Satisfaction with Use of the Topical Pain-Relieving Patch

Day 14 satisfaction ratings in the TG related to specific aspects of use of the topical pain-relieving patch (scale: 1=Strongly disagree, 2=Disagree, 3=Neutral, 4=Agree, 5=Strongly agree) were 4.9 for each of "easy to apply" and "convenient," and 4.6 for each of "preferred over pills/oral medication" and "preferred over other pain-relieving treatments (creams, gels, roll-ons, sprays, patches, and rubs)." Overall satisfaction was 4.6 out of 5 (scale: 1=not at all, 2=Not very, 3=Somewhat, 4=Very, 5=Extremely) in the TG. In the CROSSG, the mean ratings were 5.0 for "easy to apply," 4.9 for "convenient," and 4.7 for "preferred over pills/oral medication" and "preferred over

other pain-relieving treatments." Overall mean satisfaction was 4.3.

Safety

Patients in the TG and CROSSG reported no adverse events or serious adverse events while being treated with the pain-relieving patch.

Discussion

The RELIEF study reported here is a prospective, non-randomized study of patients experiencing mild to moderate acute arthritic, neurological, and musculoskeletal pain. Patients indicated a variety of medical treatments for pain at baseline and at 14 days. Medical treatments included OTC oral agents, prescription NSAIDs, opioids, anticonvulsants, skeletal muscle relaxants or a combination of the above. BPI scores indicated that patients in the treatment group were experiencing mild, moderate, or more severe pain.

In the present study, data were collected from patients at baseline and day 14 of the two-week study period. The CG showed more moderate to severe pain at baseline compared to the TG which can occur when clinical trial subjects are not specifically randomized to treatment groups. A portion of subjects opted to be in the CG initially; some investigators noted that this may have been due to a patient lack of confidence from preconceived notions about the effectiveness of a topical treatment (The higher pain scores in the CG may have influenced those patients not to enroll in a topical analgesic study for fear of treatment failure). The notable analgesic responses seen in the CROSSG group challenges those preconceived notions and offers some insights as to the potential benefit of topical treatments to patients with higher pain scores.

Changes in BPI pain severity and pain interference scores and use of concurrent pain medications from baseline to day 14 were evaluated to assess effectiveness of topical analgesics for the treatment of acute pain. This study showed that treatment with a pain-relieving patch led to a reduction in mean scores for BPI pain severity and pain interference. The comparison of changes from baseline BPI pain severity (49% v 12%) and pain interference (58% v 14%) between the TG and CG was statistically significant. A high percentage of patients in the TG reported significantly lower use of concurrent pain medications at day 14. When evaluating changes in ibuprofen, acetaminophen, and Voltaren at day 14, there was a reduction in these adjuvant analgesics in the TG of 24%, 39%, and 62%, respectively. There

were no side effects reported with the topical pain-relieving patch. Although there were no adverse events reported by patients during the 14 days of treatment, any adverse events, such as skin irritation, which has been noted in some studies after longer-term use of a topical patch, require further study for appropriate evaluation.

In this study, patients were asked to provide their response to treatment and their perceptions of improvement in various QoL parameters, satisfaction of treatment, and functionality. Patients in the TG group demonstrated an 87.5% increase in pain relief with a statistical separation from the 12% improvement in control group. It is often difficult for clinicians to determine what level of analgesia constitutes clinically meaningful relief for patients. Farrar et al[45] have reported on patient responder rates and noted that a 30% improvement in pain intensity represents changes that are clinically meaningful to patients. In addition, a measure known as the Minimal Clinically Important Improvement (MCII) has been used to define meaningful relief with various medications including topical nonsteroidal analgesics.[46,47] The MCII represents a patient's perception of what is an important improvement. It can be defined as the smallest change in measurement that signifies an important improvement. Patient reported outcome measures such as responder rate and MCII should be included in analgesic studies as changes in function and QoL are difficult to measure with numeric pain ratings. This type of information would conform to recent FDA guidance which promotes the use of data from observational studies to capture real-world evidence of changes in patient perception – which is often lacking in traditional clinical trials.[48]

The potential benefits of opioid and NSAID sparing are critical in our current climate of analgesic overuse. Although prescribing of opioids has plateaued or decreased in recent years, from 1999–2018, more than 232,000 people died in the United States from overdoses involving prescription opioids.[49,50] In addition to abuse, addiction, and overdose-related deaths with opioids, oral NSAIDs can also cause serious AEs including gastrointestinal bleeding, cardiovascular and renal complications.[51,56]

Results from this IRB-approved observational study suggest that topical pain-relieving patches may provide an effective and safe treatment alternative to conventional therapies including opioids, prescription/OTC NSAIDs, and acetaminophen for the management of mild-moderate, and chronic pain. Controlled trials are suggested to confirm these results.

Limitations

This was an observational study based on a sample of patients attending diverse clinical settings for the treatment of acute arthritic, neurological, and musculoskeletal pain who consented to participate in this study. There were differences between the CG and TG in baseline measures of type of primary pain complaint, BPI mean pain severity and interference scores, and self-reported use of concurrent pain medications. Generalizability of the findings may be limited to the TG only because those patients received topical therapies.

Pain complaints and changes in use of concurrent pain medications were reported by patients in both the CG and TG. In a few instances, there were patients who did not complete the follow up surveys after baseline. These patients' data were removed from evaluation. The direct comparison between the CG and TG is not matched regarding type and location of primary pain complaints. The lack of consistency and availability of matched data in the composition of the CG and TG could affect the accuracy of these results.

Conclusion

These results suggest that the topical pain-relieving patches studied were effective and safe for the relief of mild to moderate pain attributed to arthritis, neurological conditions, and musculoskeletal disorders. Reductions in the interference of pain were noted as well as an overall decrease in concomitant medications. These results support the use of this analgesic pain-relieving patch as a first-line treatment and should be considered for future pain management guidelines as part of multimodal pain treatment regimens.

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