

Analgesic Potential Comparison Between Piperine-Combined Curcumin Patch and Non-Piperine Curcumin Patch: A Pragmatic Trial on Post-Cleft Lip/Palate Surgery Pediatric Patients

Tantry Maulina^{1,2}, Yohanes Yoppy Purnomo³, Nadya Khamila⁴, Devy Garna⁵, Endang Sjamsudin¹, Arief Cahyanto⁶

¹Oral and Maxillofacial Surgery Department, Faculty of Dentistry, Universitas Padjadjaran, Bandung, Indonesia; ²Dentistry Department, Radboud University, Nijmegen, the Netherlands; ³Faculty of Dentistry, Maranatha Christian University, Bandung, Indonesia; ⁴Oral Surgery and Maxillofacial Specialist Program, Faculty of Dentistry, Universitas Padjadjaran, Bandung, Indonesia; ⁵Periodontology Department, Faculty of Dentistry, Universitas Padjadjaran, Bandung, Indonesia; ⁶Department of Restorative Dentistry, Faculty of Dentistry, Universiti Malaya, Kuala Lumpur, Malaysia

Correspondence: Tantry Maulina, Dentistry Department, Radboud University, Nijmegen, Gelderland, the Netherlands, Email tantry.maulina@unpad.ac.id; tantry.maulina@radboudumc.nl

Purpose: Despite its well-acknowledged analgesic potential, curcumin's low bioavailability has been recognized. Piperine, a substance naturally contained in pepper, has been known for its effect on increasing curcumin bioavailability. To investigate the analgesic potential of curcumin and piperine addition to curcumin patch used as adjuvant therapy in the management of acute postoperative orofacial pain.

Patients and Methods: This pragmatic trial recruited 75 patients that underwent oromaxillofacial surgery at Unpad Dental Hospital, Bandung, Indonesia. Research participants were randomly assigned to three different groups: the first group that did not receive any intervention other than the post-operative standard treatment (POST), the second group that received POST and non-piperine curcumin patch, and the third group that received POST and piperine-combined curcumin patch. Participants' pain intensity was evaluated by using the face, leg, activity, cry, and consolability (FLACC) pain scale and salivary prostaglandin-E₂ (PGE₂) level for two-time points, which were eight hours apart. All data were gathered and analyzed to compare the within and between-group differences.

Results: Within groups comparison of the FLACC scores for two evaluation points showed significant differences for all groups ($p < 0.01$). For salivary PGE₂ analysis, a comparison of the non-piperine group to the piperine group also showed significant results. Yet, when all three groups were compared, regardless of the differences, the results were not statistically significant.

Conclusion: Despite of the proven efficacy of curcumin patch, the addition of piperine to the curcumin patch in the current study did not provide any significant effects. Further investigation is of importance.

Keywords: curcumin, piperine, acute postoperative pain, oromaxillofacial surgery, cleft lip, cleft palate

Introduction

Young children with cleft lip and cleft palate disorders must go through operative measures early in life, risking them experiencing acute post-operative pain.¹⁻³ Previous studies about the occurrence of acute post-operative pain in children reported that 40% of children who underwent surgery experienced acute postoperative pain.⁴⁻⁶ Pain experienced by children at such a young age has a certain level of difficulty and complexity,⁷ considering that children under the age of 36 months are not able to express the pain intensity and pain type. A cross-sectional study conducted by Mekonnen et al, revealed that an experience of moderate to severe postoperative pain in children is associated with psychological, physiological, and emotional adverse effects.⁶ Considering the impact of acute post-operative pain, the management of such pain should be as adequate, immediate, and effective as possible.

The management of acute postoperative pain used to revolve around the usage of opioids. Yet, the usage of opioids has been associated with several side effects namely gastrointestinal effects such as nausea and vomiting, respiratory depression, hyperpathia, tolerance, and addiction.^{8–10} One of the natural ingredients that have been acknowledged for its therapeutic effects with less or no side effect is curcumin, a substance naturally contained in turmeric. Curcumin has been known for its multiple therapeutic potentials, including its analgesic potentials.^{11–16} As an analgesic agent, including in the orofacial region, curcumin has been evaluated and delivered in several forms, capsule, gel, paste, powder, as well as in a form of a patch.^{17,18} A previous study revealed that transdermal delivery of an analgesic agent, will eliminate unwanted side effects such as sedation and cognition. Additionally, curcumin delivered in a form of a transdermal patch has better optimization.¹⁹

The analgesic potential of curcumin is accomplished through several pathways, including the arachidonic acid metabolism and the cyclooxygenase pathway, which is related to the production of prostaglandin-E2 (PGE₂).^{20,21} PGE₂ has been known for its role in inducing pain due to inflammation. An increased level of PGE₂ has been associated with increased pain and the inhibition of PGE₂ will suppress the inflammation process and therefore, will alleviate the pain.^{22–24} Yet, regardless of its acknowledged analgesic potential, curcumin is known for its low bioavailability.^{25–27} To enhance curcumin's bioavailability, researchers have proposed several methods, including the addition of piperine.^{27,28} Piperine is an alkaloid (a chemical compound that contains mainly nitrogen atoms) found in black pepper (*Piper nigrum*), long pepper (*Piper longum*), and other *Piper* species.^{29,30} Piperine is also known for its pharmacological potentials, including its anti-inflammatory potential. When combined with curcumin, piperine acts as a bioenhancer and has been known for its effect on improving curcumin's bioavailability.^{31–33} And higher bioavailability is known to be associated with higher drug efficacy.³⁴

Based on the results of these previous studies and theories, the hypotheses were as follows: 1) curcumin patch will show high analgesic potential in managing acute postoperative pain due to inflammation, and 2) a piperine-combined curcumin patch will have better efficacy compared to a non-piperine curcumin patch in managing acute postoperative pain due to inflammation. Therefore, the current study aimed to evaluate the efficacy of (non-piperine) curcumin patch and a piperine-combined curcumin patch in managing acute postoperative pain in post cleft lip or cleft palate surgery pediatric patients. Considering the vulnerability of the subjects of the current study and the complexity of pain management in young children, the study was designed in a pragmatic setting where all subjects would still receive the postoperative pain management procedure according to hospital regulations and standard operational procedure, where the curcumin patch was given as adjuvant therapy.

Materials and Methods

Seventy-five young (41 male; 34 female) participants (mean age: 13.6 months old) who went through a cleft palate or cleft lip operative procedure for the first time namely palatoplasty (for cleft palate correction) and labioplasty (for cleft lip correction) were recruited in this pragmatic study that was conducted from the year 2022 to 2023. Prior to the start of the study, ethical clearance was gained from the Universitas Padjadjaran Research Ethics Committee (No. 083/UN6.KEP/EC/2022). The current study was conducted in full accordance with the World Medical Association Declaration of Helsinki and has been registered at the clinical trial registry with the following registration number: UMIN000053305. Consequently, the parents/ legal guardian of the participants signed an informed consent regarding their approval for the participation of their children in this study as well as their approval of their involvement in future scientific publications as the result of their participation in the current study.

Inclusion and Exclusion Criteria

Participants were included in this study if they met the following inclusion criteria: aged 36 months old or less; had an initial pain score of (a minimum of) 1 (according to the FLACC pain score); not allergic to curcumin and/or piperine and did not have any injuries or inflammation at other areas of the body that might act as another source of pain. Additionally, participants that consumed another analgesic agent aside from the ones prescribed or removed the patch (those who were assigned to the treatment groups) before eight hours of application, will be excluded from the study.

Sample Size Calculation

The sampling in this study was carried out by using a non-probability sampling technique with a purposive sampling type. The sample size calculation was performed by using a $Z\alpha$ of 5%, indicating a $Z\alpha$ value of 1.64, according to the Z table. The $Z\beta$ value was set at 20%, indicating a $Z\beta$ value of 0.84. A standard deviation (S) was calculated and set at 20, while the minimum difference ($X_1 - X_2$) that was considered significant was set at 10. When incorporated into the sample size calculation formula, the sample size calculation generated a minimum sample size of 25 samples for each group. Therefore, the minimum number of subjects needed for this study was 75.

Randomization and Blinding

Participants were randomly assigned into one of the three groups once by using a closed envelope. Seventy-five closed and sealed envelopes that contain 25 number “1” (representing the control group), 25 number “2” (representing the treatment group that received a non-piperine curcumin patch), and 25 number “3” (representing the treatment group that received the piperine-combined curcumin patch) were prepared in a random sequence. Once the patient gave consent to their participation in the study, one envelope was chosen, and the patient was assigned to one of the groups based on the number in the envelope. Our #1 field researcher guided this process and noted down the number of the group each participant was assigned to, and together with our #2 field researcher, performed the placing of the curcumin patch accordingly. Consequently, our #3 and #4 field researcher performed the pain evaluation without having any knowledge about which participant belonged to which group.

Face, Leg, Activity, Consolability, and Cry (FLACC) Pain Scale

The FLACC pain scale is a validated scale that has been widely and commonly used for acute pain evaluation on post-surgery children aged as young as two months old to seven years old that are not capable of communicating their pain. The scale evaluates five components that are considered valid indicators for pain quantification, which are facial expression, the position of the legs, bodily activities, crying characteristics of the patients, and the consolability state of the patients. Each of these components should be quantified by providing a score of 0, 1, or 2, as described in the scale. The lowest score on the scale would be “0” which indicates the patient is not experiencing any pain, and the highest score would be 10, indicating the high intensity of pain experienced by the patient.^{35–38}

Curcumin Patches

The non-piperine curcumin patch (5 × 10 cm in size) was formulated and prepared at the Pharmacy Faculty of Universitas Padjadjaran, Bandung, Indonesia from a mixture of curcuminoid extract (a product of an Indonesian herbal company named Sidomuncul), nipagin, hydroxypropyl methylcellulose (HPMC), ethyl cellulose (EC), nipasol, 95% ethanol, polyvinylpyrrolidone (PVP), and Tween 80. The preparation of the patch has been described in the previous study.¹⁹ This non-piperine patch was placed on the middle of the patient’s chest (Figure 1) who were assigned to this treatment group for eight hours before it was removed.

Another curcumin patch used in this study was the piperine-combined patch used that was produced by OMNI Global Labs, USA, with a size of 5 × 3 cm. The patch contains 110 mg of turmeric extract (95% curcuminoid) and 10 mg of piperine. The patch was placed on the upper left chest of the patient (Figure 2) with the same duration as the non-piperine curcumin patch.

Study Design

To increase external validity, the study was conducted in a pragmatic setting where the curcumin patch acted as an adjuvant therapy to an existing post-operative procedure while still applying randomization to the study. Once the patient agreed to participate, the patient was assigned to one of the following groups: a) the control group, which was the group that did not receive any intervention; b) treatment group 1, the group that received a non-piperine curcumin patch; and c) treatment group 2, the group that received piperine-combined curcumin patch. All participants received suppository Ketoprofen as the main analgesic agent (participants who weighed less than 10 kg received 50 mg of suppository Ketoprofen and those who weighed 10 kg or more received 100 mg of suppository Ketoprofen). The first dose of Ketoprofen was administered upon completion of surgery (immediately after the anesthesia effect wore off, right before



Figure 1 Placement of non-piperine curcumin patch on the middle of the chest.

participants were sent to their room for post-operative observation), and the second one was 8 hours after the first administration. For those who were assigned to the treatment group, the curcumin patch was immediately placed once the anesthesia effect had worn off. The study design can be viewed in [Figure 3](#).

Pain Evaluation

Pain evaluation was performed by measuring the acute post-operative pain immediately after the anesthesia effect wore off (identified as T_0) and eight hours after the first measurement (identified as T_1).¹⁸ In the first pain evaluation, the FLACC score was measured by our #3 field researcher followed by our #4 field researcher who performed the salivary PGE₂ sample collection (please see Salivary PGE₂ collection and evaluation). Once the salivary PGE₂ was collected, the curcumin patch was placed (for those in the treatment group). For participants in the control group, once the saliva sample was collected, no other treatment was given. Eight hours after this first evaluation, a second FLACC scoring was performed, and a second saliva sample collection was collected by the same field researchers. Once these pain evaluation measures were completed, the curcumin patch was removed.

Salivary PGE₂ Collection and Evaluation

Salivary PGE₂ level was quantified by analyzing the saliva sample collected from the patient by using the Salivette, a cotton swab that has been prepared to stimulate saliva production. Saliva collection and sample preparation were performed according to the manufacturer's instruction and as described in the previous study.³⁹ It was performed by our field researcher under the supervision of a clinical staff of the Clinical Pathology Laboratory of Hasan Sadikin Hospital. Once the saliva sample was collected, the sample was brought by the clinical staff to the Clinical Pathology Laboratory of Hasan Sadikin Hospital, Bandung, Indonesia, and was analyzed by using the Enzyme-linked of Immunosorbent Assay



Figure 2 Placement of piperine-combined curcumin patch on upper-left of the chest area of the patient (as pointed by the blue arrow).

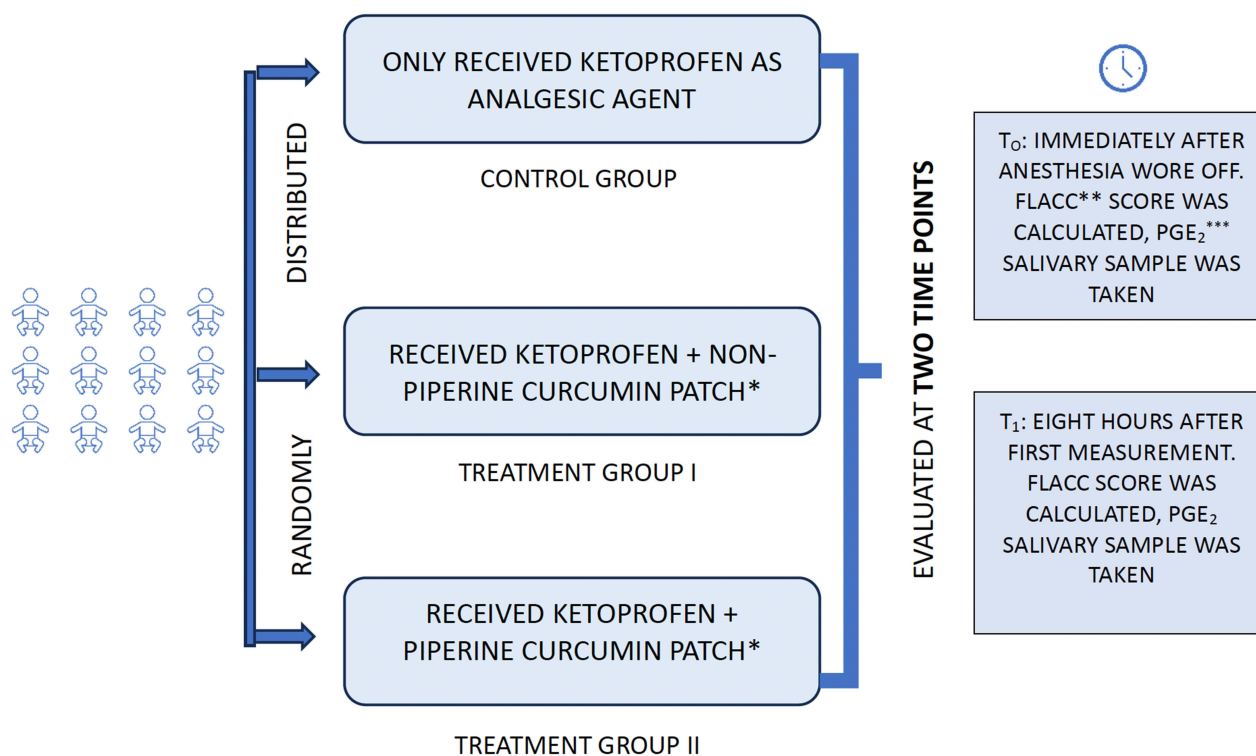
(ELISA) technique. The usage of a salivette for saliva sample collection and the analysis of salivary PGE2 by using the ELISA technique have been described in previous studies.^{39–41}

Data Analysis

All data in the current study were collected and tested for normality by using SPSS version 28 (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp). The normality test was performed by using the Shapiro–Wilk normality test. Results of the normality test showed that some of the data were not normally distributed and therefore when comparing all groups, the Kruskal–Wallis test was used. A two-group comparison was also performed and referring to the normality test results of the data, either an independent *t*-test or Mann–Whitney test was in use. Additionally, when comparing a before and after effect between two evaluation times, a Wilcoxon signed-rank test was used. A cross-tabulation analysis was also used to have a descriptive analysis of the means or standard deviation based on the independent variable(s).

Results

The results of the current study showed that youngest participants were three months old, and the eldest was 36 months old. It was also revealed that severe pain was more likely to be observed in male participants compared to female participants (Table 1). Additionally, more female participants seemed to experience less pain compared to the male participants at eight hours post-surgery evaluation time. The demographic and clinical characteristics of the participants can be viewed in Table 1.



*Curcumin patch was placed after the first measurement took place

**FLACC: Face, Leg, Activity, Consolability, and Cry pain scale

***PGE₂: Prostaglandin-E₂

Figure 3 Study design.

A descriptive analysis of the participants' distribution based on sex revealed that male participants were most likely to experience moderate to severe pain. After a descriptive analysis of the demographic and clinical characteristics of the participants, the difference of the FLACC scores and PGE₂ level were analyzed. The FLACC scores and the salivary

Table 1 Participants' Distribution Based on Demographical and Clinical Characteristics

Variable	Distribution of Participants Based on Sex		
	Male	Female	Total*
Age			
0–12 months	21 (28%)	21 (28%)	42 (56%)
13–24 months	16 (21.3%)	8 (10.7%)	24 (32%)
25–36 months	4 (5.3%)	5 (6.7%)	9 (12%)
Procedure			
Labioplasty	20 (26.7%)	24 (32%)	44 (58.7%)
Palatoplasty	21 (28%)	10 (13.3%)	31 (41.3%)
Weight			
0–8 kilograms	20 (26.7%)	20 (26.7%)	40 (53.3%)
9–16 kilograms	21 (28%)	14 (18.7%)	35 (46.7%)

(Continued)

Table 1 (Continued).

Variable	Distribution of Participants Based on Sex		
	Male	Female	Total*
Procedure Duration			
0–200 minutes	22 (29.3%)	23 (30.7%)	45 (60%)
201–400 minutes	19 (25.3%)	11 (14.7%)	30 (40%)
FLACC scoring T ₀ **			
Mild pain (0–3)	3 (4%)	5 (6.7%)	8 (10.7%)
Moderate pain (4–6)	21 (28%)	14 (18.7%)	35 (46.7%)
Severe pain (7–10)	17 (22.7%)	15 (20%)	32 (42.7%)
FLACC scoring T ₁ ***			
Mild pain (0–3)	22 (29.3%)	23 (30.7%)	45 (60%)
Moderate pain (4–6)	15 (20%)	10 (13.3%)	25 (33.3%)
Severe pain (7–10)	4 (5.3%)	1 (1.3%)	5 (6.7%)

Notes: *Percentage calculation=number of participants (n)/total number of participant (75) X 100%. **T₀= First measurement of the FLACC scale, after anesthesia effect wore off. ***T₁ = eight hours after the first measurement.

PGE₂ level means for the control group, non-piperine group, and piperine group was displayed in the box plot chart as described in Figures 4 and 5.

From Figure 4, a comparison of the FLACC scores on the initial pain evaluation time (T₀) and eight hours after the initial evaluation (T₁) showed a high reduction of pain intensity. Yet, the PGE₂ level does not show the same tendency

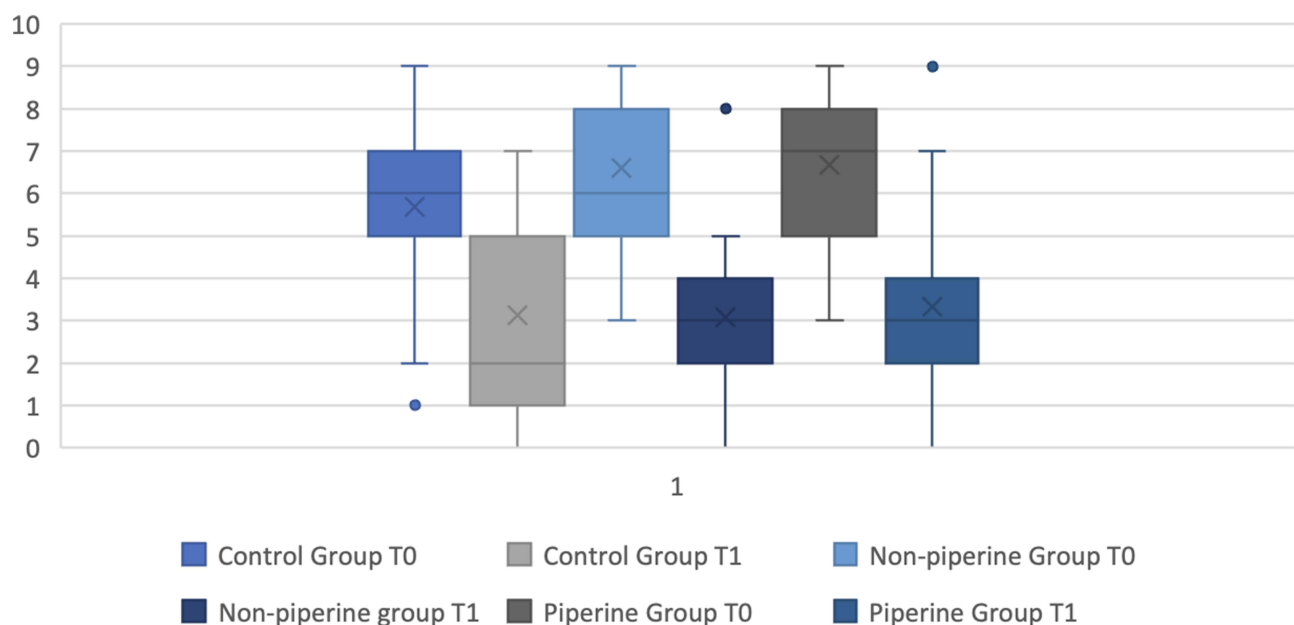


Figure 4 FLACC scores and means (showed by the "X" sign in the middle of the boxplots) for the control group, the treatment group that received a non-piperine curcumin patch, and the treatment group that received a piperine-combined curcumin patch, on two pain evaluation points (T₀= Immediately after anesthesia effect wore off, and T₁= eight hours after T₀).

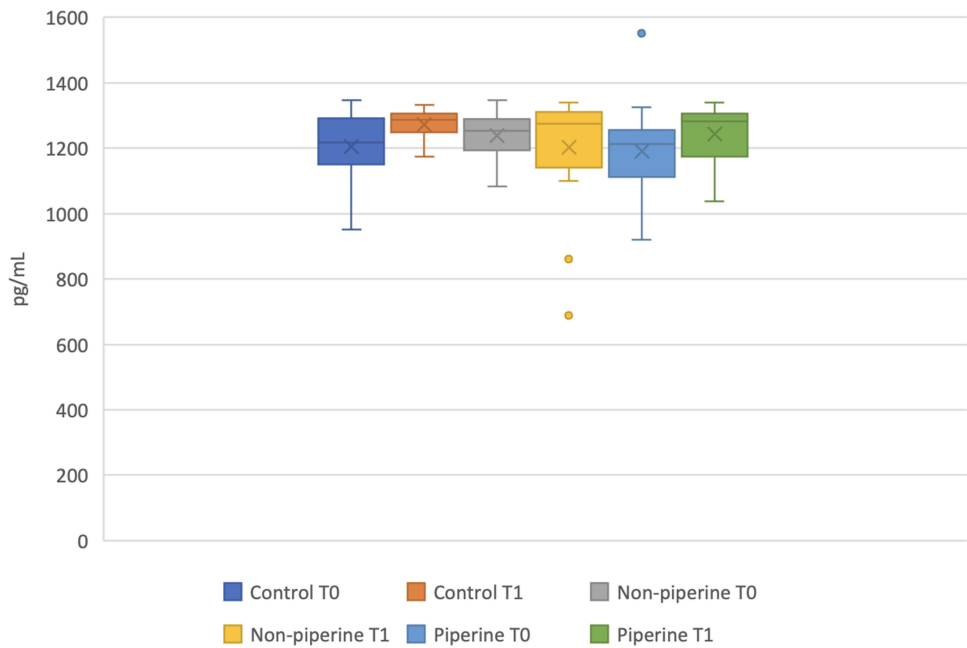


Figure 5 Salivary PGE₂ values (pg/mL) and means (showed by the “X” sign in the middle of the boxplots) for the control group, the treatment group that received a non-piperine curcumin patch, and the treatment group that received a piperine-combined curcumin patch, on two pain evaluation points (T₀= Immediately after anesthesia effect wore off, and T₁= Eight hours after T₀).

(Figure 4) where significant differences were hardly observed. The next analysis was performed by comparing the mean value of the FLACC scores and PGE₂ level based on the first evaluation time (T₀) and the second evaluation time (T₁). The comparison performed for all the groups can be viewed in Table 2.

Table 2 Within Group Comparison for the Mean Value of FLACC Scores and PGE₂ Level on Different Evaluation Time

FLACC score			
Group	Evaluation time*		p-value**
	T ₀	T ₁	
Control	5.68 (SD=2.08)	3.12 (SD= 2.19)	<0.001***
Non-Piperine	6.60 (SD=1.78)	3.08 (SD=1.68)	<0.001
Piperine	6.68 (SD=1.95)	3.32 (SD=2.10)	<0.001
Salivary PGE ₂ level (in pg/mL)			
Group	Evaluation time		p-value
	T ₀	T ₁	
Control	1205.25 (SD= 104.88)	↑ 1273.32 (SD= 44.89)	0.002
Non-Piperine	1238.25 (SD= 68.57)	1203.41 (SD= 166.33)	0.716
Piperine	1191.56 (SD= 127.78)	↑ 1242.66 (SD= 78.78)	0.083

Notes: *T₀= Immediately after the anesthesia wore off; T₁= Eight hours after T₀. **Significance level p < 0.05. Wilcoxon signed-rank test. ***Bold values indicate significant statistical test results and/or increased values.

Table 3 Between Groups Analysis for FLACC and PGE₂ Measurements for the Control Group, Treatment Group 1 (Non-Piperine), and Treatment Group 2 (Piperine)

Variable	p-value*
FLACC score	
Control compared to non-piperine curcumin patch (Mann–Whitney test)	0.06
Control compared to piperine combined curcumin patch (Independent t-test)	0.15
Non-piperine curcumin patch compared to piperine-combined curcumin patch (Mann–Whitney test)	0.88
Between groups (Kruskal–Wallis test)	0.12
Salivary PGE ₂ level (in pg/mL)	
Control compared to non-piperine curcumin patch (Mann–Whitney test)	0.01**
Control compared to piperine combined curcumin patch (Independent t-test)	0.47
Non-piperine curcumin patch compared to piperine-combined curcumin patch (Mann–Whitney test)	0.01
Between groups (Kruskal–Wallis test)	0.06

Notes: *Significance level: $p < 0.05$. **Bold values indicate significant statistical test results.

Based on the analysis results displayed in Table 2, the current study found that when the FLACC scores from the first evaluation point were compared to the second evaluation point, the pain intensity was all significantly decreased. Yet, there were some variabilities observed in the results of the salivary PGE₂ whereas the salivary PGE₂ level of the control group and the piperine group were found to be increasing at the second evaluation time. In the control group, the increased PGE₂ level was quite high that it yielded a significant difference.

The final analysis in the current study was the between-group analysis that was performed in two ways. The first analysis performed was to evaluate the effect of piperine on curcumin efficacy by comparing one group to another group (ie, control group to non-piperine group, non-piperine group to piperine group). The second analysis was by comparing all three groups together. The results of the analysis are displayed in Table 3.

The information contained in Table 3 was in general, in line with the information displayed in Table 2. The analysis of the PGE₂ level showed significant differences when the PGE₂ level of the non-piperine group was compared to the control group ($p = 0.01$) as well as the piperine group ($p = 0.01$). These results were also in line with the previous analysis considering that there was an increase in the PGE₂ level of the control group and the piperine group.

Discussion

Pain intensity experienced by the participants that was quantified by the FLACC pain scale showed only eight participants experienced mild pain at the first pain evaluation point. This finding is supported by research conducted by Mekonnen et al, that showed the prevalence of moderate to severe acute postoperative pain experienced by pediatric patients can be as high as 40.5% (95% CI: 32.7–48.4).⁶ Additionally, it was also revealed that more male participants experienced more moderate and severe pain compared to female participants. This finding is in line with the results finding of Mwashambwa et al, about the prevalence of post-surgery pain, where the male sex was associated with severe pain.⁴² Another study has also shown how female infants with preterm history showed a more robust facial expression than male infants when it comes to acute procedural pain,⁴³ indicating sexual differences in pain response, which might

explain the findings of the current study where male participants showed higher pain according to the FLACC, a scoring scale that is based on one of which, facial expression.^{35,36}

Regarding the within-group analysis, a comparison of the FLACC scores showed that pain scores decreased in all three groups significantly. As known, all participants in the current study received suppository Ketoprofen as a standard post-operative analgesic agent, which may have taken into effect the participant's pain behavior. An animal study about the effect of ketoprofen on pain behaviors after an incision revealed that ketoprofen has a modality-specific effect when it comes to pain behavior, causing a more calming effect on pain,⁴⁴ which may explain the decreased FLACC scores, considering that FLACC pain scoring is based on pain behavior.^{38,45} For participants in the treatment group, curcumin and piperine effect might have also given additional effects on pain reduction, as shown in previous studies.^{46–48}

Alongside FLACC scoring, pain evaluation was also performed by analyzing the salivary PGE₂ level. Interestingly, the results of the salivary PGE₂ level analysis did not show the same tendency as the FLACC scores, whereas the salivary PGE₂ level of the control group and the piperine group showed an increase at the second evaluation time. On the contrary, participants in the non-piperine curcumin patch showed a decreased salivary PGE₂ level, indicating the possible effect of the curcumin patch as adjuvant therapy. To note, even though an increase in salivary PGE₂ level was also detected in the treatment group that received a piperine-combined curcumin patch, it was not as high as the one shown in the control group, indicating the possible effect of piperine-combined curcumin patch. Interestingly, regardless of the above-mentioned effect of the piperine-combined patch on the salivary PGE₂ level, the addition of piperine to curcumin in the current study did not provide curcumin with the expected superiority. A comparison between the non-piperine curcumin patch group and the piperine-combined patch group showed a significant difference, where the non-piperine curcumin patch group showed more pain reduction.

In regard to the non-detected effect of piperine addition to curcumin, the difference in curcumin originality might have played a significant role. A previous study revealed that curcumin grown in different areas showed different qualities.^{49–51} Additionally, curcumin extraction and preparation might also play a role in its efficacy.^{52,53} As the current study used patches that originated from different areas, there might be potential differences in efficacy, with the non-piperine curcumin patch being the more superior one, clouding the supposedly advantageous effect of piperine addition to curcumin. Concerning the different sizes of the patches, the piperine-combined patch contains nanoparticles of curcumin, which has been acknowledged for its high efficacy.^{54,55} Therefore, regardless of its smaller size, the piperine-combined patch was expected to have comparable efficacy to the non-piperine patch, which, even though bigger in size, contains microparticles curcumin instead of nanoparticles curcumin.

The difference between the FLACC scores and the salivary PGE₂ levels in this study might be due to the assessment method. The FLACC score assessment was performed by an observation method, with no intervention or action that might induce anxiety or additional pain in participants. On the other hand, regardless of the non-invasiveness, saliva collection might induce anxiety or additional pain that affects the salivary PGE₂ level,⁵⁶ considering that saliva collection required the operator to put the cotton swab in the patient's oral cavity. A similar finding was reported by Momesso et al, that investigated salivary PGE₂ levels after third molar surgery. Regardless of the analgesic agents consumed by the participants, an increase in salivary PGE₂ level was still detected 48 hours after surgery.⁵⁷

In addition to what has already been covered, each person's reaction to pain could also be a complicating element. Since experiencing pain is a subjective experience, people's reactions to it will always vary. To ensure that the pain level was assessed objectively, we used a validated pain scale (the FLACC) and a blinded-calibrated examiner combined with the measurement of a biomarker. And in order to guarantee accurate sample collection, we employed a skilled field researcher under the guidance of knowledgeable medical personnel. The usage of Ketoprofen as the main analgesic agent was inevitable as it is part of the standard procedure, and we would like to use the pragmatic setting in our study. However, since Ketoprofen was administered to each participant, it was regarded as the baseline condition, and the assessment of pain level was deemed trustworthy as a result.

Considering the results of the current study, the usage of curcumin patch as an adjuvant agent for post-cleft lip/palate surgery pediatric patients is considered clinically relevant. The curcumin patch can be combined with the standardized non-opioid post-surgery analgesic agents for pediatric patients, namely Ketoprofen (as used in our hospital). This recommendation is in line with the results of a study conducted by Do et al, where the usage of non-opioid pain

management showed better results compared to opioid-related pain management.⁵⁸ Based on the findings of current studies, more studies comparing the efficacy of non-opioid analgesic agents involving natural ingredients for post-operative pain management in pediatric patients should be expected. Additionally, considering the rather contradictory results of previous studies and the current study, further studies investigating the potential benefit of piperine addition to curcumin as an analgesic agent should be anticipated as well.

Study Limitation

The patches used in the current study did not use curcumin from the same sources. Due to some technical difficulties, the pharmacy lab at our university was not able to prepare the piperine-combined curcumin patch as planned, which was the reason why the current piperine-combined curcumin patch came to use. Further evaluation investigating the efficacy of piperine addition to curcumin that originated from the same area might reveal different result(s).

Conclusion

The findings of the current study suggested that a non-piperine curcumin patch showed potential analgesic effect as hypothesized. Yet, piperine addition to curcumin (patch) did not provide curcumin with the expected result. The efficacy of the piperine-combined curcumin patch was not higher than the non-piperine curcumin patch.

Data Sharing Statement

All data will be available upon request to corresponding author.

Acknowledgment

The abstract of this paper was intended for presentation at the FDI World Congress 2023 Conference, however was not presented. The poster's abstract was published in 'Abstracts of the 2023 FDI World Dental Congress' in International Dental Journal: <https://www.sciencedirect.com/science/article/pii/S0020653923003027>. All authors would like to acknowledge the medical staff of Unpad Dental Hospital, Bandung, Indonesia, and the Oral and Biomaterial Research Unit of the Faculty of Dentistry, University of Padjadjaran, Bandung, Indonesia for their kind assistance during the research period. We would also like to acknowledge University of Padjadjaran, Bandung, Indonesia for funding this study through the Riset Kompetensi Dosen Unpad research grant.

Disclosure

The authors report no conflict of interest in this work.

References

1. Bandyopadhyay KH, Paul A. Postoperative analgesia for cleft lip and palate repair in children. *J Anaesthesiol Clin Pharmacol*. 2016;32(1):5–11. doi:10.4103/0970-9185.175649
2. Tasman SGR, Putri FA, Maulina T. Validation of the Indonesian Version of the Face, Legs, Activity, Cry, Consolability (FLACC) scale in postoperative cleft lip and/or cleft palate patients. *Open Dent J*. 2022;16:1–6.
3. Augsornwan D, Pattangtanang P, Pikhunthod K, Surakunprapha P. Postoperative pain in patients with cleft lip and palate in srinagarind hospital. *J Med Assoc Thai*. 2011;94(Suppl 6):S118–23.
4. Pérez EV, Lizama GR, Cárdenas VG. Current trends and new strategies in acute postoperative pain management in children. *Medic Res Arch*. 2021;9:9. doi:10.18103/mra.v9i9.2539
5. Moura LA, Pereira LV, Manamisava R, Borges NC, Castral TC, Souza LAF. Severe acute postoperative pain self-reported by children after ambulatory surgeries: a cohort study. *Rev Bras Enferm*. 2021;74(Suppl 4):2.
6. Mekonnen ZA, Melesse DY, Kassahun HG, Flatie TD, Workie MM, Chekol WB. Prevalence and contributing factors associated with postoperative pain in pediatric patients: a cross-sectional follow-up study. *Periop Care Operating Room Manage*. 2021;23:100159. doi:10.1016/j.pcorrm.2021.100159
7. Srouji R, Ratnapalan S, Schneeweiss S. Pain in Children: assessment and Nonpharmacological Management. *Int J Pediatr*. 2010;2010:474838. doi:10.1155/2010/474838
8. Sadhasivam S, Chidambaran V, Olbrecht VA, et al. Opioid-related adverse effects in children undergoing surgery: unequal burden on younger Girls with higher doses of opioids. *Pain Med*. 2015;16(5):985–997. doi:10.1111/pme.12660
9. Wang H, Duan C, Zhang J, et al. Evaluation of the effect of perioperative administration of S(+)-ketamine hydrochloride injection for postoperative acute pain in children: study protocol for a prospective, multicenter, randomized, open-label, parallel-group, pragmatic clinical trial. *Trials*. 2022;23(1):586. doi:10.1186/s13063-022-06534-z

10. White LD, Hodge A, Vlok R, Hurtado G, Eastern K, Melhuish TM. Efficacy and adverse effects of buprenorphine in acute pain management: systematic review and meta-analysis of randomised controlled trials. *British J Anaesth*. 2017;120(4):668–678.
11. Jakubczyk K, Drużga A, Katarzyna J, Skonieczna-żydecka K. Antioxidant potential of curcumin-A meta-analysis of randomized clinical trials. *Antioxidants*. 2020;9(11):1.
12. Ojo OA, Adeyemo TR, Rotimi D, et al. Anticancer Properties of Curcumin Against Colorectal Cancer: a Review. *Front Oncol*. 2022;12:881641. doi:10.3389/fonc.2022.881641
13. Adamczak A, Ożarowski M, Karpiński TM. Curcumin, a natural antimicrobial agent with strain-specific activity. *Pharmaceuticals*. 2020;13(7):1.
14. Peng Y, Ao M, Dong B, et al. Anti-inflammatory effects of curcumin in the inflammatory diseases: status, limitations and countermeasures. *Drug Des Devel Ther*. 2021;15:4503–4525. doi:10.2147/dddt.S327378
15. Shep D, Khanwelkar C, Gade P, Karad S. Safety and efficacy of curcumin versus diclofenac in knee osteoarthritis: a randomized open-label parallel-arm study. *Trials*. 2019;20(1):214. doi:10.1186/s13063-019-3327-2
16. Zhao G, Shi Y, Gong C, et al. Curcumin Exerts antinociceptive effects in cancer-induced bone pain via an endogenous opioid mechanism. *Original Research Front Neurosci*. 2021;15:1–10. doi:10.3389/fnins.2021.696861
17. Kriplani P, Guarve K, Baghel US. Novel herbal topical patch containing curcumin and arnica montana for the treatment of osteoarthritis. *Curr Rheumatol Rev*. 2020;16(1):43–60. doi:10.2174/1573397115666190214164407
18. Stermiczuk B, Rossouw PE, Michelogiannakis D, Javed F. Effectiveness of curcumin in reducing self-rated pain-levels in the orofacial region: a systematic review of randomized-controlled trials. *Int J Environ Res Public Health*. 2022;19(11):1.
19. Kriplani P, Guarve K, Singh Baghel U. Formulation optimization and characterization of transdermal film of curcumin by response surface methodology. *Chin Herb Med*. 2021;13(2):274–285. doi:10.1016/j.chmed.2020.12.001
20. Sahebkar A, Henrotin Y. Analgesic efficacy and safety of curcuminoids in clinical practice: a systematic review and meta-analysis of randomized controlled trials. *Pain Med*. 2015;17(6):1192–1202. doi:10.1093/pm/pnv024
21. Moini Zanjani T, Ameli H, Labibi F, Sedaghat K, Sabetkasaei M. The attenuation of pain behavior and serum COX-2 concentration by curcumin in a rat model of neuropathic pain. *Korean J Pain*. 2014;27(3):246–252. doi:10.3344/kjp.2014.27.3.246
22. Xue P, Wang S, Lyu X, et al. PGE2/EP4 skeleton interoception activity reduces vertebral endplate porosity and spinal pain with low-dose celecoxib. *Bone Res*. 2021;9(1):36. doi:10.1038/s41413-021-00155-z
23. Jang Y, Kim M, Hwang SW. Molecular mechanisms underlying the actions of arachidonic acid-derived prostaglandins on peripheral nociception. *J Neuroinflamm*. 2020;17(1):30. doi:10.1186/s12974-020-1703-1
24. Sugita R, Kuwabara H, Kubota K, et al. Simultaneous inhibition of PGE₂ and PGI₂ signals is necessary to suppress hyperalgesia in rat inflammatory pain models. *Mediators Inflamm*. 2016;2016:9847840. doi:10.1155/2016/9847840
25. Tabanelli R, Brogi S, Calderone V. Improving curcumin bioavailability: current strategies and future perspectives. *Pharmaceut*. 2021;13:1.
26. Gupta T, Singh J, Kaur S, Sandhu S, Singh G, Kaur IP. Enhancing bioavailability and stability of Curcumin Using Solid Lipid Nanoparticles (CLEN): a covenant for its effectiveness. Original Research. *Front Bioengineer Biotechnol*. 2020;8. doi:10.3389/fbioe.2020.00879
27. Mimica B, Bučević Popović V, Banjari I, Jeličić Kadić A, Puljak L. Methods used for enhancing the bioavailability of oral curcumin in randomized controlled trials: a meta-research study. *Pharmaceuticals*. 2022;15(8):1.
28. Prasad S, Tyagi AK, Aggarwal BB. Recent developments in delivery, bioavailability, absorption and metabolism of curcumin: the golden pigment from golden spice. *Cancer Res Treat*. 2014;46(1):2–18. doi:10.4143/crt.2014.46.1.2
29. Derosa G, Maffioli P, Sahebkar A. Piperine and its role in chronic diseases. *Adv Exp Med Biol*. 2016;928:173–184. doi:10.1007/978-3-319-41334-1_8
30. Rather RA, Bhagat M. Cancer chemoprevention and piperine: molecular mechanisms and therapeutic opportunities. *Front Cell Dev Biol*. 2018;6:10. doi:10.3389/fcell.2018.00010
31. Wang R, Han J, Jiang A, et al. Involvement of metabolism-permeability in enhancing the oral bioavailability of curcumin in excipient-free solid dispersions co-formed with piperine. *Int J Pharmaceut*. 2019;561:9–18. doi:10.1016/j.ijpharm.2019.02.027
32. Patil VM, Das S, Balasubramanian K. Quantum chemical and docking insights into bioavailability enhancement of curcumin by piperine in pepper. *J Physic Chem A*. 2016;120(20):3643–3653. doi:10.1021/acs.jpca.6b01434
33. Liu Z, Smart JD, Pannala AS. Recent developments in formulation design for improving oral bioavailability of curcumin: a review. *J Drug Deliver Sci Technol*. 2020;60:102082. doi:10.1016/j.jddst.2020.102082
34. Niederberger E, Parnham MJ. The impact of diet and exercise on drug responses. *Int J Mol Sci*. 2021;22(14):1.
35. Kochman A, Howell J, Sheridan M, et al. Reliability of the faces, legs, activity, cry, and consolability scale in assessing acute pain in the pediatric emergency department. *Pediatr Emerg Car*. 2017;33(1):14–17. doi:10.1097/pec.0000000000000995
36. Crellin DJ, Harrison D, Santamaria N, Huque H, Babl FE. The psychometric properties of the FLACC scale used to assess procedural pain. *J Pain*. 2018;19(8):862–872. doi:10.1016/j.jpain.2018.02.013
37. Matsuishi Y, Hoshino H, Shimojo N, et al. Verifying the validity and reliability of the Japanese version of the Face, Legs, Activity, Cry, Consolability (FLACC) Behavioral Scale. *PLoS One*. 2018;13(3):e0194094. doi:10.1371/journal.pone.0194094
38. Redmann AJ, Wang Y, Furstin J, Myer CM, de Alarcón A. The use of the FLACC pain scale in pediatric patients undergoing adenotonsillectomy. *Int J Pediatr Otorhinolaryngol*. 2017;92:115–118. doi:10.1016/j.ijporl.2016.11.016
39. Agossa K, Dubar B, Lemaire G, et al. Effect of lactobacillus reuteri on gingival inflammation and composition of the oral microbiota in patients undergoing treatment with fixed orthodontic appliances: study protocol of a randomized control trial. *Pathogens*. 2022;11(2):1.
40. Lorenzo-Pouso AI, Pérez-Sayáns M, Bravo SB, et al. Protein-based salivary profiles as novel biomarkers for oral diseases. *Dis Markers*. 2018;2018:6141845. doi:10.1155/2018/6141845
41. Maan AS, Patil AK. Assessment of salivary interleukin-1 β (IL-1 β), prostaglandin E(2) (PGE(2)) levels and pain intensity in children and adults during initial orthodontic treatment. *J Orthod Sci*. 2019;8:16. doi:10.4103/jos.JOS_13_19
42. Mwashambwa MY, Yongojo IM, Kapalata SN, Meremo AJ. Post-operative pain prevalence, predictors, management practices and satisfaction among operated cases at a regional referral hospital in dar es salaam, Tanzania. *Tanzania J Health Res*. 2018;20(2):1–8.
43. Guinsburg R, de Araújo Peres C, Branco de Almeida MF, et al. Differences in pain expression between male and female newborn infants. *Pain*. 2000;85(1–2):127–133. doi:10.1016/s0304-3959(99)00258-4
44. Spofford CM, Ashmawi H, Subieta A, et al. Ketoprofen produces modality-specific inhibition of pain behaviors in rats after plantar incision. *Anesth Analg*. 2009;109(6):1992–1999. doi:10.1213/ANE.0b013e3181bbd9a3

45. Shabana T, Ibrahim A. The revised-Face, Leg, Activity, Cry, and Consolability scale: an Egyptian version. Original Article. *Res Opinion Anesth Intens Care*. 2018;5(1):67–71. doi:10.4103/roaic.roaic_36_17
46. Phoolcharoen N, Oranratanaphan S, Ariyasriwatana C, Worasethsin P. Efficacy of curcuminoids for reducing postoperative pain after laparoscopic gynecologic surgery: a pilot randomized trial. *J Complement Integr Med*. 2019;16(4):2.
47. Basu P, Maier C, Basu A. Effects of curcumin and its different formulations in preclinical and clinical studies of peripheral neuropathic and postoperative pain: a comprehensive review. *Int J Mol Sci*. 2021;22(9):4666.
48. J-W Y, Li S, Bao L-D, Wang L. Piperine treating sciatica through regulating inflammation and MiR-520a/P65 pathway. *Chinese J Nat Med*. 2021;19(6):412–421. doi:10.1016/S1875-5364(21)60040-7
49. Setyawati A, Pujiasmanto B, Fatawi A, Batubara I. Secondary metabolites of turmeric and ginger on various altitudes and soil characteristics. *IOP Confer Series*. 2021;724(1):012020. doi:10.1088/1755-1315/724/1/012020
50. Shi S Assessment of Turmeric (*Curcuma longa* L) varieties for yield and curcumin content. Auburn University; 2020. Available from: <https://etd.auburn.edu/bitstream/handle/10415/7399/Shanheng%20Shi.pdf?sequence=2>. Accessed May 18, 2024.
51. Singh S, Joshi RK, Nayak S. Identification of elite genotypes of turmeric through agroclimatic zone based evaluation of important drug yielding traits. *Industr Crops Product*. 2013;43:165–171. doi:10.1016/j.indcrop.2012.07.006
52. Zheng B, McClements DJ. Formulation of more efficacious curcumin delivery systems using colloid science: enhanced solubility, stability, and bioavailability. *Molecules*. 2020;25(12). doi:10.3390/molecules25122791
53. Urošević M, Nikolić L, Gajić I, Nikolić V, Dinić A, Curcumin MV. Biological activities and modern pharmaceutical forms. *Antibio*. 2022;11(2). doi:10.3390/antibiotics11020135
54. Chopra H, Dey PS, Das D, et al. Curcumin nanoparticles as promising therapeutic agents for drug targets. *Molecules*. 2021;26(16). doi:10.3390/molecules26164998
55. Hettiarachchi SS, Dunuweera SP, Dunuweera AN, Rajapakse RMG. Synthesis of curcumin nanoparticles from raw turmeric rhizome. *ACS Omega*. 2021;6(12):8246–8252. doi:10.1021/acsomega.0c06314
56. Famitafreshi H, Karimian M. Prostaglandins as the agents that modulate the course of brain disorders. *Degener Neurol Neuromuscul Dis*. 2020;10:1–13. doi:10.2147/dnnd.S240800
57. Momesso GAC, Grossi-Oliveira GA, Silva WPP, et al. A triple-blind randomized clinical trial of different associations between dexamethasone and non-steroids anti-inflammatories for preemptive action in third molar extractions. *Sci Rep*. 2021;11(1):24445. doi:10.1038/s41598-021-04068-z
58. Do A, Rorison E, Borucki A, Shibata GS, Pomerantz JH, Hoffman WY. Opioid-free pain management after cleft lip repair. *Plast Reconstr Surg Glob Open*. 2023;11(9):e5259. doi:10.1097/gox.00000000000005259

Publish your work in this journal

The Journal of Pain Research is an international, peer reviewed, open access, online journal that welcomes laboratory and clinical findings in the fields of pain research and the prevention and management of pain. Original research, reviews, symposium reports, hypothesis formation and commentaries are all considered for publication. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/journal-of-pain-research-journal>