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ORIGINAL RESEARCH

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

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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-E_2 (PGE_2) 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.

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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 (PGE_2).[20,21] PGE_2has been known for its role in inducing pain due to inflammation. An increased level of PGE_2 has been associated with increased pain and the inhibition of PGE_2will 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 Zα of 5%, indicating a Zα value of 1,64, according to the Z table. The Zβ value was set at 20%, indicating a Zβ 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

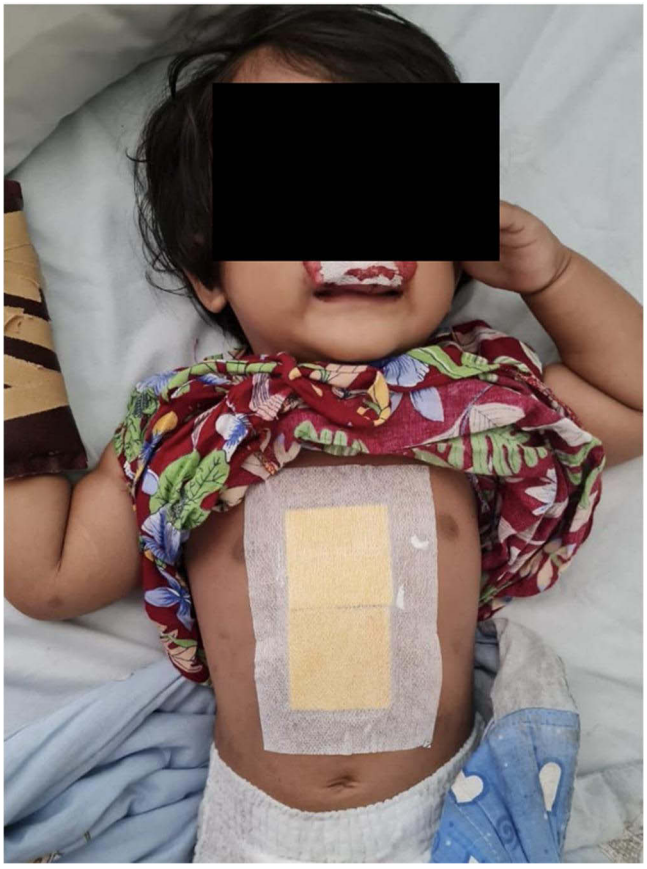

Figure 1 Placement of non-piperine curcumin patch on the middle of the chest.

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 PGE_2 sample collection (please see Salivary PGE2 collection and evaluation). Once the salivary PGE_2 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 PGE_2 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 sand 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

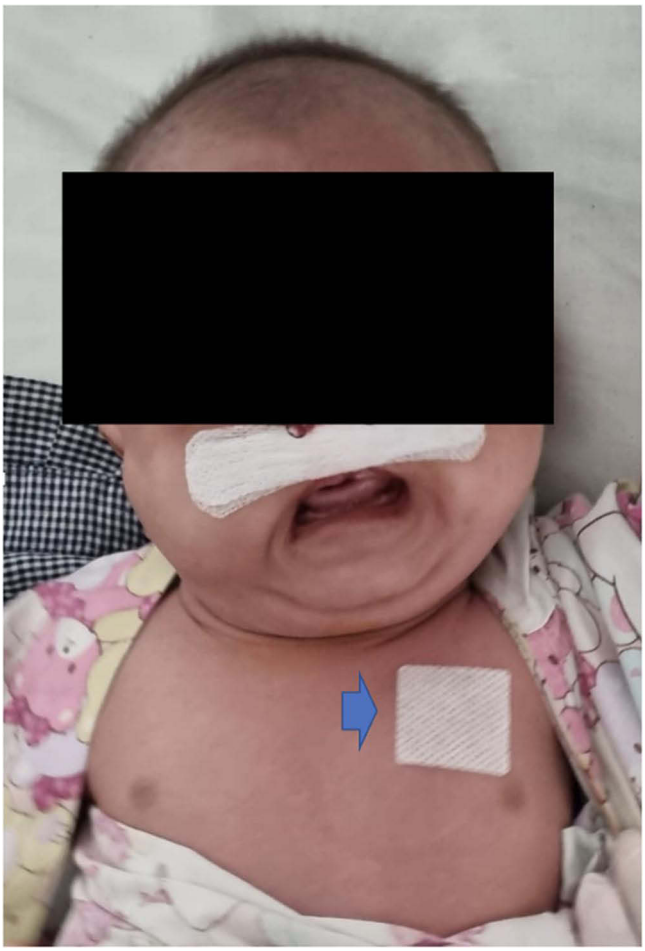

Figure 2 Placement of piperine-combined curcumin patch on upper-left of the chest area of the patient (as pointed by the blue arrow).

(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.

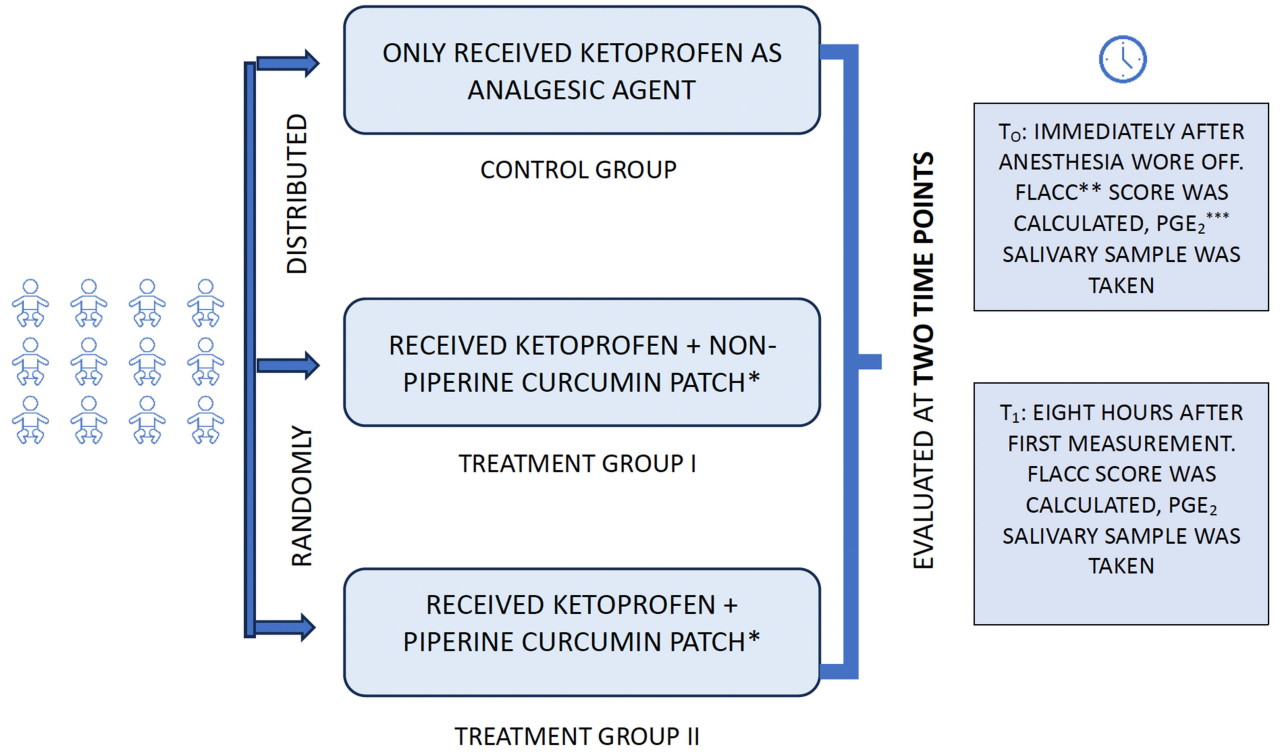

Figure 3 Study design.

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 dan 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%. **T_0= First measurement of the FLACC scale, after anesthesia effect wore off. ***T_1 = 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 (T_0) and eight hours after the initial evaluation (T_1) showed a high reduction of pain intensity. Yet, the PGE_2 level does not show the same tendency

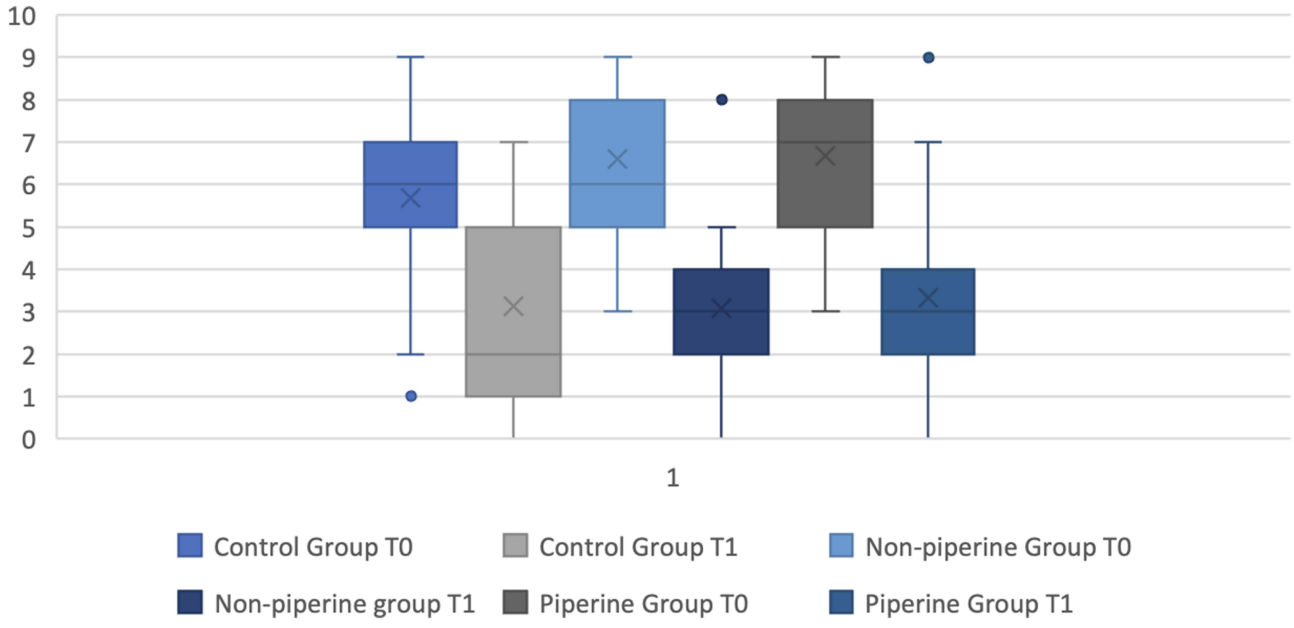

Figure 4 FLACC scores and means (showed by the "**X**" sign in the middle of the boxplots) for the control group, the treatment group that received a non-piperine curcumin patch, and the treatment group that received a piperine-combined curcumin patch, on two pain evaluation points (T_0= Immediately after anesthesia effect wore off, and T_1= eight hours after T_0).

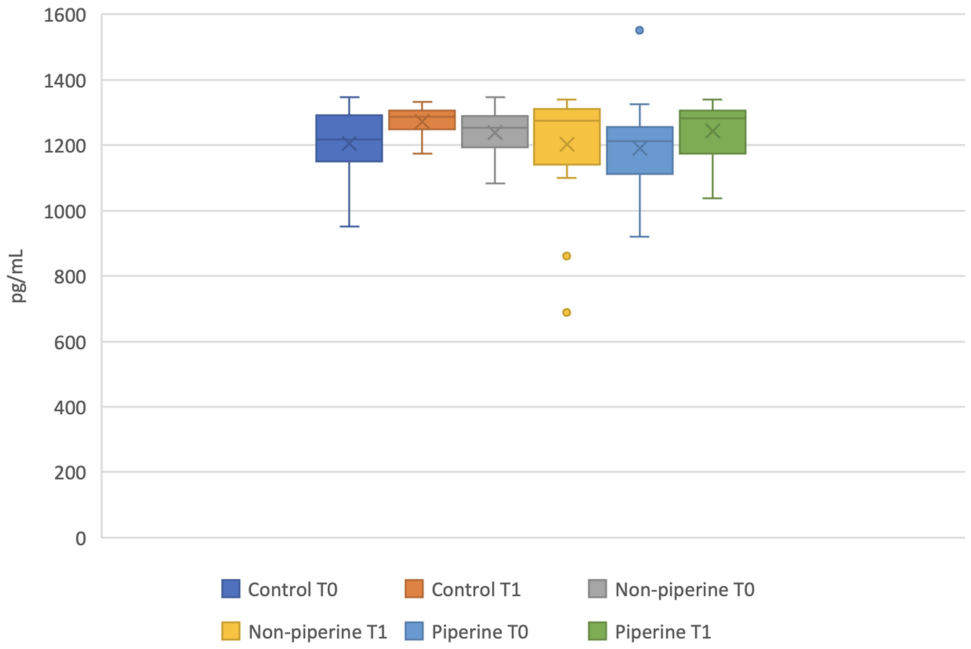

Figure 5 Salivary PGE_2 values (pg/mL) and means (showed by the "**X**" sign in the middle of the boxplots) for the control group, the treatment group that received a non-piperine curcumin patch, and the treatment group that received a piperine-combined curcumin patch, on two pain evaluation points (T_0= Immediately after anesthesia effect wore off, and T_1= Eight hours after T_0).

(Figure 4) where significant differences were hardly observed. The next analysis was performed by comparing the mean value of the FLACC scores and PGE_2 level based on the first evaluation time (T_0) and the second evaluation time (T_1). 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 PGE_2 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: *T_0= Immediately after the anesthesia wore off; T_1= Eight hours after T_0. **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 PGE_2 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 PGE_2 whereas the salivary PGE_2 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 PGE_2 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 PGE_2 level showed significant differences when the PGE_2 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 PGE_2 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 PGE_2 level. Interestingly, the results of the salivary PGE_2 level analysis did not show the same tendency as the FLACC scores, whereas the salivary PGE_2 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 PGE_2 level, indicating the possible effect of the curcumin patch as adjuvant therapy. To note, even though an increase in salivary PGE_2 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 PGE_2 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 PGE_2 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 PGE_2 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 PGE_2 levels after third molar surgery. Regardless of the analgesic agents consumed by the participants, an increase in salivary PGE_2 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.

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Disclosure

The authors report no conflict of interest in this work.

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