Original Article

Assessing the Effectiveness of Different Modes of Diclofenac in Post-Endodontic Pain Management: A Randomized Controlled Clinical Study

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ABSTRACT

Background

The main factor for most people to routinely seek endodontic therapy is pain. However, the pain may still be reported after the endodontic therapy. Thus, the use of pre-operative analgesics has been shown to reduce the onset of postoperative pain.

Objectives

The study was planned to assess the effectiveness of pretreatment with diclofenac in managing post-endodontic pain while comparing the efficacy of two modes of delivery systems i.e. oral, and transdermal patches.

Material and methodology

A randomized controlled trial was done on 180 adult subjects with irreversible pulpitis. The patients were aggregated into three groups: Oral (group B) and transdermal (group C) administration of diclofenac was done in patients just before undergoing any endodontic treatment. While in (group A) acetaminophen, a rescue pill was administered to the patients. The pain was gauged using "*Visual Analog Scale* (VAS)" and the pain frequency was measured at 8, 12, 24, 48 and 72 hours after the endodontic treatment in all three groups that were analysed statistically.

Results

VAS was greater for the oral Diclofenac groups than the control group. On inter-group comparison between the groups control and the oral Diclofenac, it was seen that there was no significant variation at the end of 8, 12, 24, 48 and 72 hrs. At 8 hours, there was a significant variance between the groups transdermal patch and the oral Diclofenac [*p=.036*], with a greater change in the VAS in transdermal patch than in the oral diclofenac group. On inter-group comparison between the Control group and the Transdermal Patch, There was a significant variance between the two groups at 12, 24, 48, 72 hours, with p=.040, p=.009, p=.001 and p=.002 respectively.

Conclusion

A promising analgesic technique for the treatment of endodontic pain appears to be the transdermal diclofenac patch. The study places a strong emphasis on using preoperative analgesics to lessen post-endodontic pain.

Keywords

Analgesics; Diclofenac; Endodontic treatment; Pre- and Post-treatment; Transdermal patch.

INTRODUCTION

The main factor for most people to routinely seek endodontic therapy is pain. Endodontic treatment assists in restoring a tooth that has been permanently damaged by bacterial invasion and infection.[1] The treatment's main

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goal is to completely remove the infected and necrotic pulp tissue from the root canal space and seal it off from the outside world. Before a proper and successful endodontic procedure, there is a significant reduction in discomfort.[2-6]

The discomfort may not, however, be completely and immediately relieved. Most patients receive some degree of rapid postoperative pain reduction as a result of the root canal procedure, but 30% of them do so due to the lingering effects of inflammation.[5] So, an endodontic treatment should take into consideration both the patient's primary concerns and any potential long-term adverse effects, like postoperative pain.

During an endodontic procedure, the first 24 hours are typically when postoperative pain is at its worst. Over the next 3 to 7 days, the levels gradually drop.[5-7] Various chemicals are produced as a result of the body's innate immunological reaction to tissue damage or injury. Prostaglandin is produced from the arachidonic acid metabolite by cyclooxygenase enzymes 1 and 2. The afferent nociceptors get sensitized by the converted prostaglandins, which lowers the pain threshold. Consequently, the primary goals of pharmaceutical therapies are to inhibit cyclooxygenases, therefore reducing the generation of prostaglandins and the sensitivity of nerve fibres.[8-10] Postoperative pain is a side effect of conventional dental operations, but root canal therapy has the highest.[11] An extreme inflammatory response and infection result from procedural situations.[12] Endodontic pain is managed with a variety of drugs including "NSAIDs (non-steroidal anti-inflammatory drugs)". Prostaglandin production at the sites of inflammation is primarily inhibited as part of the mechanism of action.[13]

NSAIDs have been used to relieve postoperative pain in endodontics in a number of clinical studies, but the outcomes have been mixed. While some research indicate that providing non-narcotic analgesics has a positive effect, others assert that there are no effective results.[14] Opioids and drug combinations are some of the additional medications used in combination with NSAIDs to alleviate endodontic pain. When the medications were provided both preoperatively and postoperatively to alleviate the endodontic pain, previous research produced contradictory results.[15,16]

Treatment of Pain before endodontic treatment

Oral analgesics provide a practical and efficient way to treat even the most severe dental pain when rapid access to final care is not possible. Medications like ibuprofen an NSAID-class medication have been the most thoroughly examined. It works by inhibiting the COX enzymes.[2] Ibuprofen's highest daily dosage recommendation is 3200 mg, with typical doses of 400 to 800 mg every 4 to 8 hours. The lowest effective dosage should be used because the most common adverse effects, such as gastrointestinal discomfort, are dose-dependent. Moreover, caution must be taken while giving NSAIDs to people who have heart illness. Ibuprofen use in the 30 days preceding the incident is linked to a 30% increased risk of myocardial infarction.[11] Even in people who have taken ibuprofen for only a brief period of time, these concerns can still occur, especially at dosages higher than 1200 mg per day. Nonetheless, NSAIDs, including ibuprofen, exhibited a lower risk of cardiovascular illness.[12,13]

Acetaminophen interacts with cannabinoid and serotonergic receptors in the brain and blocks prostaglandin production peripherally. The maximum daily dose of acetaminophen advised by the manufacturer is 3000 mg. The lowest effective dose is advised since acetaminophen carries a risk of hepatotoxicity.[14] Complexes of codeine, hydrocodone, oxycodone, and tramadol are examples of medications in the opioid class. These medications modify pain perception by centrally acting on mu and kappa receptors. The hazards of abuse and addiction, as well as the restrictions and regulations that have been put in place to restrict their use, advocate avoiding these drugs wherever feasible.[13-16]

The Oxford league table shows that NSAIDs are more effective than opioids for treating severe dental pain.[16] The treatment of severe dental pain has been demonstrated to be more effective when NSAIDs and acetaminophen are used together than when either medicine is used alone. Ibuprofen and acetaminophen should be administered simultaneously as it has been demonstrated to be more effective than taking them in alternate courses and should be promoted.[17,18]

Patients with endodontic pathology often have hours of pain relief from local anesthetics and oral painkillers, especially when longer-acting medications like bupivacaine are used. Furthermore, when employed as a component of selective anesthesia, the injection of local anesthetics may further assist to promote an accurate diagnosis. Antibiotics are ineffective painkillers, whereas oral painkillers and local anesthetics are quite useful in controlling preoperative pain. Clinicians

should only provide these medications in cases of unchecked, widespread infection or when a medical condition calls for their preventive usage.[19-22]

Post-operative Pain Control

In endodontics, perioperative pain control revolves around achieving profound local anesthetic. Unfortunately, patients with significant endodontic pain, particularly those with symptomatic irreversible pulpitis, may have trouble getting enough pulpal anesthetic.[23-25] Some patients' perioperative pain may not be sufficiently controlled by local anesthetic alone. In certain situations, additional pharmacologic drugs might be utilized to boost its effectiveness. The analgesic effects of nitrous oxide itself can enhance the effectiveness of local anesthetic treatments.[26-28]

Managing Post-operative Pain

Although endodontic pathology's final treatment is the best way to eliminate acute pain, some postoperative discomfort is expected. After endodontic therapy, most patients only experience minor discomfort that has little effect on day-to-day activities. Just 6% of patients experience more severe pain after therapy, which is consistent with a surgical flare-up. Following endodontic treatment, patients indicate that the majority of their pain symptoms disappear in a few days. Hence these symptoms are informed and managed.[22-28]

Similar to how preoperative pain is treated; postoperative pain is best treated with oral drugs, such as ibuprofen and acetaminophen combination therapy. To assure pain management during the immediate postoperative phase, when pain can be the worst, long-acting anesthetics such as bupivacaine are helpful adjuncts. Studies in the medical literature show that bupivacaine can prolong analgesia even after it has reached its half-life. The bioavailability and potency of existing medications may be improved by newer formulations.[26-31]

Endodontic treatment is critically dependent on the deterrence and management of pain that occurs after the root canal therapy. To determine the efficacy of pretreatment analgesics in managing post-endodontic pain, this study compared the efficacy of two routes of analgesic delivery: oral and transdermal patches.

MATERIALS AND METHODOLOGY

One hundred and eighty subjects between the ages of 18 and 65 were chosen from those attending the Dental Clinics at the College of Dentistry at Prince Sattam Bin AbdulAziz University and after obtaining ethical clearance from the Institutional Review Board of our University (IRB no.: REC-HSD- 015-2022). The patient's demographic information and a comprehensive history of the presenting illness were documented before treatment. Patient's consent was obtained and the study was conducted in accordance with the ethical standards laid down in 1964, by the Declaration of Helsinki, and revised in 2000.

The study comprised patients who reported pain in the mandibular molars and were given the diagnosis of irreversible pulpitis, which can be treated endodontically in a single visit. Patients with known allergies to anti-inflammatory medications, known sensitivity to diclofenac, pregnant or breastfeeding women, patients with a history of asthma, and patients with stomach or intestinal issues were also excluded from the trial. The study did not include any teeth that had periapical infections of any kind.

The subjects who fulfilled the inclusion criteria were selected and aggregated into one of three groups (60 each) after they were explained about the study design and the consent was taken.

- **GROUP A** (Control group) patients were given only a rescue pill (Acetaminophen) in cases they developed pain after undergoing root canal treatment.
- **GROUP B:** Oral diclofenac group, where patients took diclofenac tablet orally right before undergoing root canal treatment.
- **GROUP C:** Transdermal diclofenac patch group, where patients were placed transdermal patch on the arm just before undergoing root canal treatment.

Procedure:

Root canal treatment in all the groups was done in a single visit and the severity of postoperative pain was calculated using VAS score after 8, 12, 24, 48 and 72 hours. Patients were given a rescue pill (Acetaminophen) in case they developed pain. A feedback form (Visual Analog Scale) was given to the patient and he/she was contacted through telephone call to remind him/her to fill the feedback form. Follow-up was done for 72 hours.

Criteria for the assessment of pain:

Pain was assessed using "*Visual Analog Scale"*

- **No pain:** Patient did not have any pain after treatment (0)

- **Distressing pain**: Discomforting, but bearable (1-7)
- **Severe pain**: Difficult to bear (8-10)

Statistical Analysis:

The three groups were analysed statistically using the Wilcoxon signed ranks test and Mann-Whitney test. Intra-group comparison at various time intervals was done using the Wilcoxon Signed Ranks Test. Intergroup comparison was done using the Mann-Whitney test. A 0.05 p-value was deemed statistically significant for statistical interpretation.

RESULTS

The comparisons were made between the control and the oral Diclofenac groups in table1 with 60 subjects in each group. The change in the VAS for the control group from the base level-BL to various hours as seen as means is at 8, 12, 24, 48 and 72 hours is 8.61, 9.96, 7.96, 8.06, and 7.81 respectively. While for the oral Diclofenac group the VAS change from the base level to at 8, 12, 24, 48 and 72 hours is 12.41, 11.06, 13.06, 12.96, and 13.21 respectively. It is evident the change in VAS was greater for the oral Diclofenac groups than the Control group. **Table 1**

Table 1: In Groups A (Control) and B (Oral Diclofenac) comparison where subjects (N) = 60

Changes in VAS	Group	Mean Rank	Sum of Ranks
VAS (BL-8 hrs)	Control (C)	8.61	86.10
	Oral Diclofenac (OD)	12.41	124.10
VAS (BL-12 hrs)	C	9.96	99.51
	OD	11.06	110.51
VAS (BL-24 hrs)	C	7.96	79.51
	OD	13.06	130.51
VAS (BL-48 hrs)	C	8.06	80.51
	OD	12.96	129.51
VAS (BL-72 hrs)	C	7.81	78.10
	OD	13.21	132.10

On inter-group comparison between the groups i.e. Control and the Oral Diclofenac, it was seen that there was no significant variation at the end of 8, 12, 24, 48 and 72 hours, after the endodontic procedure from the base level as depicted by the P values: .936, .225, .069, .409, and .082 respectively. **Table 2**

TABLE 2: Comparing the efficacy between Groups A (Control) and B (Oral Diclofenac)

	VAS (hours)					
	Pre-operative	8	12	24	48	72
Mann-Whitney U	32.001	50.001	35.501	27.501	40.501	29.501
Wilcoxon W	88.001	105.001	90.501	82.501	95.501	84.501
Z	-1.474	-.082	-1.216	-1.825	-.829	-1.748
Asymp. Sig. (2-tailed)	.142	.936	.225	.069	.409	.082
Exact Sig. [2*(1-tailed Sig.)]	.166[a]	.972[a]	.248[a]	.076[a]	.437[a]	.106[a]

The comparisons were made between the oral diclofenac and the transdermal patch groups in Table 3 with 60 subjects in each group. In the oral Diclofenac group the VAS change from the base level at 8, 12, 24, 48 and 72 hours, is 12.41, 11.51, 13.51, 12.96, and 13.21 respectively. While for the transdermal patch group, the VAS change from the base level to at 8, 12, 24, 48 and 72 hours is 9.51, 12.80, 11.10, 12.61 and 10.51 respectively. The change in VAS was greater for the oral Diclofenac groups than the transdermal patch group at 8 hours after the treatment. Later transdermal patch subjects showed greater change than the oral Diclofenac group till 48 hours, after which the variance in the VAS was the same for both groups. **Table 3**

TABLE 3: In group B (oral diclofenac) and C (transdermal patch) comparison where subjects (N) = 60

Changes in VAS	Group	Mean Rank	Sum of Ranks
VAS (BL-8 hrs)	Oral Diclofenac (OD)	12.41	124.10
	Diclofenac Transdermal Patch(DTP)	9.51	95.10
VAS (BL-12 hrs)	OD	11.51	115.10
	DTP	12.80	128.00

Changes in VAS	Group	Mean Rank	Sum of Ranks
VAS (BL-24 hrs)	OD	13.51	131.50
	DTP	11.10	111.00
VAS (BL-48 hrs)	OD	12.96	129.60
	DTP	12.61	126.10
VAS (BL-72 hrs)	OD	13.21	132.10
	DTP	10.51	105.10

On inter-group comparison between the groups' Transdermal patch and the Oral Diclofenac, it was seen that there was no significant variation at the end of 4, 12, 24, and 48 hours. After the endodontic procedure from the base level as depicted by the P values: .745, .571, .061 and .509 respectively. At 12 hours, there was a significant variance between the groups Transdermal patch and the Oral Diclofenac [p=**.036],** with a greater change in the VAS in the transdermal patch than in the oral groups. **Table 4.**

TABLE 4: Comparing efficacy between groups B (Oral Diclofenac) C (Transdermal patch)

	VAS (hours)					
	Pre-operative	8	12	24	48	72
Mann-Whitney U	50.1	47.1	24.1	44.1	27.1	28.6
Wilcoxon W	105.1	102.1	79.1	99.1	82.1	97.6
Z	-.083	-.327	-2.104	-.569	-1.883	-.662
Asymp. Sig. (2-tailed)	.936	.745	.036	.571	.061	.509
Exact Sig. [2*(1-tailed Sig.)]	.972[a]	.797[a]	.044[a]	.632[a]	.076[a]	.530[a]

The comparisons were made between the control and the Transdermal Patch groups in Table 5 with 60 subjects in each group. The change in the VAS for the control group from the base level-BL to various hours as seen as means is at 8, 12, 24, 48 and 72 hours, is 8.61, 9.96, 7.96, 8.06, and 7.81 respectively. While for the Transdermal Patch group the VAS change from the base level to at 8, 12, 24, 48 and 72 hours, is 9.51, 12.76, 11.01, 12.61 and 10.51 respectively. It is evident the change in VAS was greater for the Transdermal Patch groups than the control group. **Table 5.**

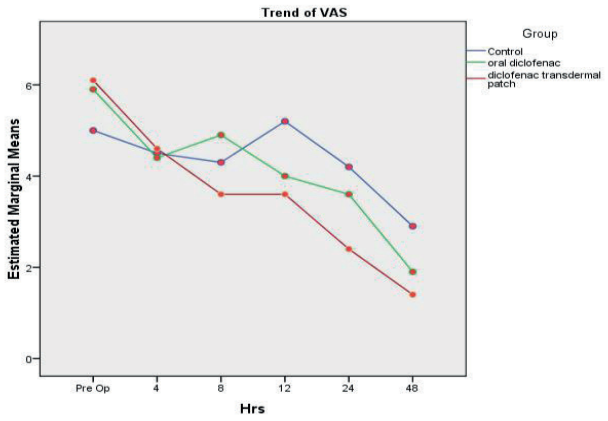
TABLE 5: In Groups A (Control) and C (Transdermal Patch) comparison where subjects (N)=60

Changes in VAS	Group	Mean Rank	Sum of Ranks
VAS (BL-8 hrs)	Control (C)	8.61	86.10
	Diclofenac Transdermal Patch (DTP)	9.51	95.10
VAS (BL-12 hrs)	C	9.96	99.60
	DTP	12.76	127.60
VAS (BL-24 hrs)	C	7.96	79.60
	DTP	11.01	110.10
VAS (BL-48 hrs)	C	8.06	80.60
	DTP	12.61	126.10
VAS (BL-72 hrs)	C	7.81	78.10
	DTP	10.51	105.10

On inter-group comparison between the groups control and the Transdermal Patch, it was seen that there was no significant variation at the end of 8 hrs, [p=.436.], after the endodontic procedure from the base level. There was a significant variance between the two groups at 12, 24, 48, 72 hrs, with p=.040, p=.009, p=.001 and p=.002 respectively. **Table 6.**

TABLE 6: Comparing the efficacy between Groups A (Control) and C (Transdermal Patch)

	VAS (Hours)					
	Pre-operative	8	12	24	48	72
Mann-Whitney U	21.501	41.501	27.001	17.001	5.001	9.501
Wilcoxon W	76.501	96.501	82.001	72.001	60.001	64.501
Z	-2.379	-.782	-2.070	-2.656	-3.624	-3.295
Asymp. (2- Sig. tailed)	.018	.436	.040	.009	.001	.002
Exact Sig. [2*(1- tailed Sig.)]	.024[a]	.483[a]	.076[a]	.010[a]	.001[a]	.002[a]



Inference:

In the control group, the pain frequency first decreased from the preoperative period to 12 hours but after 12 hours, it increased to 24 hours and then decreased to 72 hours. In oral diclofenac, the pain frequency first decreased from the preoperative period to 8 hours, then increased from 8 hours to 12 hours and then again decreased from 12 hours to 72 hours. In the diclofenac transdermal patch group, the pain frequency was continuously found to decrease from the pre-operative period until 72 hours.

DISCUSSION

Diclofenac, which has an analgesic effect, is the most often prescribed NSAID. Diclofenac transdermal patches, a novel topical drug delivery technology that has recently been developed, provide the benefit of sustained drug delivery with fewer systemic side effects because of the low plasma concentrations.[32-39] In the current investigation, oral and transdermal diclofenac patches were used to quantify postoperative endodontic pain.

For several reasons, including enhanced and better bioavailability, transdermal patches are recommended over oral routes of medication administration to systemic circulation. Patients who have trouble swallowing tablets and capsules may be tempted to smash the tablets to help them down, but doing so removes the controlled release properties of the medication. Transdermal patches are shown to be effective, safe, and efficient in delivering analgesic effects in such circumstances.[32-39]

Diclofenac is a common drug used to alleviate post-operative pain in clinical settings. In a cross-over trial, Selvi et al. associated the effectiveness of a transdermal diclofenac patch with that of intramuscular diclofenac injections for extractions. They concluded that the transdermal diclofenac patch works well to alleviate mild to moderate post-operative pain after tooth removal.[37] Bhaskar H et al., did a comparable study between oral and transdermal diclofenac administration.[35] They discovered that the transdermal patch which delivered potent analgesia and was equated to oral intake, was pleasant for the trial subjects to use. Perepa A et al. assessed the post-operative analgesic efficacy of transdermal and intramuscular diclofenac in patients undergoing orthognathic surgery. The diclofenac patch is a safe, non-invasive technique to induce analgesia in the immediate post-operative time, they emphasized.[38] The results of the current trial are in line with earlier ones and emphasize patient compliance with the patch over other drug delivery techniques.

In the current study, it was discovered that group B experienced less post-endodontic pain than group A did (i.e., group A > group b). This was because oral diclofenac is easily absorbed and hence acts quickly. Derry et al. (2015) also reported clinical benefits of utilizing diclofenac potassium that dissolves quickly and is absorbed, which provides more effective pain relief than diclofenac potassium that is absorbed more slowly.[39]

First pass metabolism in transdermal patches, according to Dhiman S et al in 2011, is another restriction on oral medication delivery that can be overcome with transdermal administration.[40] Transdermal patches, also called skin patches, use a specific membrane to control how quickly the liquid medication inside the reservoir of the patch may flow through the skin and into the bloodstream in a coordinated manner. The 50-sq. cm patch has 100 mg of diclofenac diethyl amine as its active element, allowing for a continuous release of the medicine and greater pain alleviation, according to Dhanapal S in 2016. The latest investigation also employed the same-sized patch.[41]

During all of the observational time periods in the current investigation, there was no discernible difference between the oral administration of diclofenac and the controls. In contrast, Jenarthanan et al., study found a significant variance between the oral diclofenac and the placebo groups.[42] Yet, when they utilized oral diclofenac and compared it to a placebo, Al-Rawhani et al., study showed a comparable result to the one of the present one. Only after 48 hours did diclofenac considerably

outperform the placebo in terms of VAS scoring.[43]

According to Krishnan S et al., transdermal patches use a particular type of membrane that regulates how quickly drugs are released from a reservoir inside the patch onto the skin and then into the bloodstream.[44] Comparing the pain frequency between the control and transdermal groups had a p-value of 0.435 at 4 hours, which was statistically insignificant. However, at 8, 12, 24, and 48 hours, post-operatively, the p values changed to be statistically significant with values of 0.039, 0.008, 0.000, and 0.001, respectively. In contrast, Mueller et al., study found a significant variance in the acute injuries between the placebo group and the transdermal group.[45]

Although VAS is a subjective way of measuring pain, it is quantifiable. It was selected because it was believed to provide better comparability with other studies. Patients in this study used a pain scale similar to that used by Kaufman et al., who tested slow-release methyl prednisolone, and defined pain as any degree of discomfort on a scale from 0 to 10.[47] Both investigations showed that once the extra analgesic was given, post-treatment pain decreased. The current trial found that discomfort persisted for up to 48 hours, which was consistent with the results of Mattscheck et al.,[51] and in support of Ng et al.,[9] who described a VAS of 0-5. Both the placebo and the experimental groups in the current study experienced a decreasing trend in pain intensity from baseline to 48 hours post-treatment (Fig. 1). A good indicator of diclofenac's analgesic impact is the considerable postoperative variance between the mean VAS of the control and the transdermal patch, measured from 8 to 48 hours after surgery.

The pain intensity ratings with both the oral diclofenac tablets and the transdermal patch slowly reduced from day 1 to day 2 according to an assessment of the pain intensity after root canal therapy. This conclusion is consistent with that of a prior study by Dhanapal et al.,[41] who compared the effectiveness of a single transdermal diclofenac patch dose to three oral doses taken three times a day as a pre-operative analgesic for pain control. Diclofenac transdermal patches were utilized as a post-operative analgesic after tooth extraction in the study by Bachalli PS et al.,[34] noticed a similar decrease in pain for the mandibular molars. The findings of Bhaskar H et al., [35] revealed that the oral and transdermal patch forms had comparable analgesic efficacy for the extraction of premolars. In contrast to the current study, which used endodontic therapy as the intervention, the previous investigations both used extractions as the interventional group.

There was no difference in the amount of pain reduction between the two groups when the two methods (oral and transdermal) were assessed, with the exception of at 8 hours. This is in line with the findings of a study by Murugan et al.,[33] who found that a post-treatment transdermal patch may be more efficient for managing postoperative endodontic pain than oral diclofenac. Whereas in the current investigation, the hourly variation was tracked, their groups observed the participants' VAS by giving them the medication before and after the therapy. Similar to this, Krishnan et al.,[44] assessed the efficiency of diclofenac when administered orally and trans-dermally for the treatment of post-extraction pain in extractions. Six groups were created out of the 40 patients, each with 40 non-salvageable non-tender teeth. Using the Visual Analog Scale, postoperative pain was assessed at 6 and 12 hours. The effectiveness of diclofenac sodium oral tablets versus diclofenac sodium patches in treating postoperative molar extraction pain was not significantly different.[48-50]

In the present study, a significant difference between the transdermal patch and oral Diclofenac groups was seen at 8 hours [p=.035]. To the best of our knowledge, no earlier investigations had demonstrated these findings; as a result, a comparison was challenging. In contrast, Mangal S et al., investigation which employed identical medication, reported no appreciable differences between the two methods of delivery when the VAS was measured at 4, 8, 12, and 24 hours following treatment.[32]

Limitations

The outcomes of this patient-dependent investigation were determined by the patients' subjectively recorded score values. As a result, the bias of the participant could not be removed from the research. The age range of the subjects who were involved varied greatly. Future studies might take into account using age-matched people. In the study, two delivery methods of the same NSAID (diclofenac) were examined. Further research can be done using different pharmacological substances.

CONCLUSION

It was determined, within the constraints of the current in-vivo study, that preoperative analgesics are crucial

in minimizing post-endodontic discomfort. Diclofenac transdermal patches have a potential analgesic effectiveness. In dentistry, pain is unavoidable and frequently causes problems for both the patient and the dentist. Transdermal analgesic administration could become more convenient in the future. This approach is anticipated to grow in acceptance and usage due to enhanced delivery and a wider range of analgesics. In the current investigation, diclofenac-containing transdermal patches are shown to be a potential analgesic method for treating endodontic pain. To learn more about using transdermal patches to deliver analgesics for post-endodontic pain, more research with bigger patient samples is needed.

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