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Comparison of the Preemptive Analgesic Efficacy of Submucosal and Trans dermal patch form of Diclofenac and Its Influence on Post–Operative Discomfort in Surgical Removal of Impacted Third Molars -- A Randomized control study

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ABSTRACT

Introduction aim and objectives: Diclofenac and other NSAIDs are commonly used for disimpaction in postoperative care, but their efficacy is greater when administered preemptively. Oral diclofenac is associated with risks such as gastrointestinal bleeding and cardiovascular events. Submucosal and transdermal patch formulations have been developed to reduce these risks. This study aims to compare and evaluate the preemptive analgesic efficacy of submucosal and transdermal patch forms of diclofenac in reducing postoperative discomfort in lower third molar surgery, and to assess mouth opening, VAS score, and swelling.

Material and methods : This study recruited 40 patients aged 18 to 30 and randomly divided them into Group S and Group T. Group T received 100 mg transdermal diclofenac patch 10 minutes before surgery, and Group S received 50 mg submucosal diclofenac injection 10 minutes before surgery. Pain, swelling, and mouth opening were measured preoperatively and at 1, 6, and 24 hours postoperatively. Pain was assessed using VAS, and swelling was evaluated using a 3-point scale.

Results: The study findings indicate that administering diclofenac submucosally is more effective in managing postoperative mouth opening and swelling in third molar surgeries. The researchers used a Paired T test to analyze the statistical significance of postoperative swelling and mouth opening in both groups. The results demonstrated a significant difference of 0.02 for preoperative measurements, while the remaining timeline was statistically insignificant. Moreover, a statistically significant difference of 0.03 and 0.02 for 6 and 24 hours was found for postoperative mouth opening in both groups. However, no significant difference was observed for the remaining timeline. In contrast, a statistically significant difference in postoperative pain was observed in both groups for preoperative, 1 hour, and 24-hour groups, with the results being 0.03 and 0.04.

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Discussion: The preemptive NSAIDs reducing the post operative pain by inhibiting cyclooxygenases (COX-1, COX-2) which are key in prostaglandin synthesis (Gorecki.et.al), and bypasses first-pass metabolism in the liver (Jenarthanan.et.al). Topical administration of non steroidal anti inflammatory drug offer advantange of local, enhanced drug delivery to affected tissue with lower incidence of local and systemic adverse effects due to reduced plasma concentrations.

Conclusion: To conclude, administering preemptive analgesics in the early stages of surgery is crucial for pain reduction and better results. The submucosal group has a quicker onset but shorter duration of action, with less swelling and better mouth opening than the transdermal patch group. The transdermal patch offers a slow and continuous release of the drug, resulting in prolonged effectiveness and added convenience, making it a promising method for managing pain in the immediate postoperative phase.

Keywords: *Submucosal, Diclofenac, Transdermal, Dental, Quality Of Life*

INTRODUCTION

Pain is an inevitable symptom experienced during surgery, and as such, it is a crucial concern for the surgeon. While pain is a natural defense mechanism, it can also cause harm to sensitive tissue. Effective pain management is a crucial aspect of surgical practice, and the surgical removal of third molars (1), (2) is a commonly used model for evaluating analgesic effectiveness and tolerability. Several types of analgesics (3) ,(4) are available to manage third molar impaction(5). Nonsteroidal anti-inflammatory drugs (NSAIDs)(6) like ibuprofen and diclofenac (7), (8) are commonly used due to their analgesic and anti-inflammatory properties.Other like Oral Bromelain and Serratiopeptidase (9),(10) used for swelling (11). Acetaminophen is also frequently used for pain relief, but it lacks anti-inflammatory effects. Opioids like codeine and oxycodone can be used for severe pain but are generally reserved for short-term use due to the potential for dependency and adverse effects. The choice of analgesic medication should be tailored to each individual patient's needs and medical history while weighing the potential risks and benefits.

Diclofenac, an NSAID, is a popular choice for pain management due to its analgesic and anti-inflammatory properties. It works by inhibiting the production of prostaglandins, which are responsible for pain, inflammation, and fever. However, like all NSAIDs, diclofenac carries potential risks and side effects such as gastrointestinal bleeding and major adverse cardiovascular events. Therefore, it should be used with caution and evaluated carefully in patients with a history of these conditions or other risk factors to minimize the likelihood of adverse effects (12). Diclofenac can be used preemptively to prevent pain and inflammation before surgical procedures, which has been shown to provide better pain relief than its use after surgery(13). Notwithstanding, diclofenac, similar to all nonsteroidal anti-inflammatory drugs (NSAIDs), has associated risks and side effects, such as gastrointestinal bleeding and major adverse cardiovascular events. As a result, its use should be approached with caution, and patients with a history of these conditions or other risk factors should be carefully evaluated to minimize the likelihood of adverse effects. When taken orally, there is a risk of first-pass metabolism and significant drug loss before systemic absorption. However, the submucosal route of administration and transdermal route avoids the risk of first-pass metabolism and drug loss and allows for local absorption.

Submucosal administration of diclofenac has emerged as a promising strategy for pain management after third molar surgery. A study by Gorecki et al. (14) demonstrated that submucosal diclofenac injection was effective in reducing postoperative pain intensity and duration compared to placebo. The authors also reported a faster onset of pain relief with submucosal diclofenac compared to oral administration. Brignardello-Petersen et al.(15) highlighted several advantages of submucosal

diclofenac, including higher local drug concentration and avoidance of first-pass metabolism. However, submucosal administration of diclofenac may also lead to an increased risk of postoperative bleeding, as reported by Gorecki et al. In contrast, non-invasive transdermal patches of diclofenac have gained attention as an alternative route of drug administration for pain management. Bhaskar et al.(16) reported that transdermal diclofenac patches provided effective analgesia in acute dental pain with no serious adverse effects. However, caution should be exercised in patients with sensitive skin due to potential skin irritation. Bachalli et al.(17) found that transdermal administration of diclofenac resulted in a slower onset of action but with a longer duration of action, making it a potential candidate for the management of chronic pain. Further studies comparing the efficacy and safety of submucosal and transdermal forms of diclofenac are deficient.

The aim of the study would be to compare and evaluate the preemptive analgesic efficacy of submucosal and transdermal patch forms of diclofenac in reducing postoperative discomfort in lower third molar surgery, and to evaluate the mouth opening, visual analog scale (VAS) score, and swelling.

MATERIALS AND METHODS

Study Design

This is a prospective, randomized study that enrolled 40 patients (22 female and 18 male) from the Department of Oral and Maxillofacial Surgery at Saveetha Dental College and Hospitals. Approval from the institutional ethical committee was obtained and informed consent was obtained from all participating patients. The study aimed to standardize the groups by selecting patients with impacted mandibular 3rd molar class I position A, who were under 90 kg and had American Society of Anesthesiology status I (18). The study was doubly blinded and placebo-controlled, and patients who had used sedatives, tranquilizers, or analgesic drugs within 24 hours before treatment, those with impacted mandibular 3rd molar other than class III position C, a history of sensitivity to NSAIDS or ketorol dt., bleeding disorder, or dermatological disorders were excluded from the study.

Randomization

Participants who met the inclusion criteria were randomly assigned to either the study group, which received Submucosal diclofenac, or the control group, which received transdermal diclofenac. This allocation was done using random numbers generated by a computer, with 40 opaque envelopes numbered and marked by an external individual based on the group allocated to them. These envelopes were kept by a nurse external to the research team, and study subjects randomly picked one envelope from a closed box upon presenting at the clinic. The primary researcher was informed of which protocol to use intraoperatively by the staff nurse, and the solutions were prepared and applied by the surgeon before the 3rd molar surgery.

Surgical protocol

The surgical procedure was conducted by an experienced surgeon and assistant in a controlled environment to eliminate potential operator-induced bias. In the Submucosal group, submucosal diclofenac 50mg was administered buccally, lingually, distally, and mesially to the third molar, while the transdermal diclofenac group was given a diclofenac patch (Nu patch) 100mg ten minutes before surgery. Local anesthesia was administered using the technique of regional blockade of the inferior and lingual alveolar nerves, with supplementary buccal nerve infiltration. The solution was injected carefully and slowly after negative aspiration, with a maximum volume of 3.6 ml of 2% lidocaine and 1:100,000 epinephrine. A crevicular incision was made along the second mandibular molar and third molars, and the distal relieving incision was extended along the buccal gingival sulcus to the external oblique ridge where the posterior relieving incision was placed. The Howarth's periosteal elevator was used to reflect a full thickness mucoperiosteal flap and retracted with an Austin retractor. Buccal and distal bone removal was performed using a 702 bur on a

straight hand piece with constant irrigation with 0.9% sterile normal saline solution, and guttering was done slightly beyond the furcation. The teeth were delivered with sectioning of the crown, and the socket was inspected, irrigated, and the flap sutured with 3-0 silk. Pain was evaluated using a visual analog scale (VAS) after extraction, and swelling was evaluated using a 3-point scale and mouth opening preoperatively, postoperatively at 1st hour, 6th hour, and 24 hours. Patients were also asked to score their overall pain using a visual analog pain scale preoperatively, postoperatively at 1st, 6th hour, and 24 hours. A day after surgery, patients were asked to provide an overall evaluation of their pain experience during the postsurgical follow-up visit. No patients dropped out of the study. Following removal of the impacted mandibular third molar, both groups were given a 50mg diclofenac tablet (Voveran SR) and mouthwash (19) twice daily for three consecutive days. All subjects received verbal and written post-operative instructions and were instructed to seek medical attention in the event of delayed post-extraction complications, such as uncontrolled bleeding and unbearable pain. The sutures (20) were removed seven days after surgery.

The statistical analysis of the data was performed using IBM SPSS version 23 software. Descriptive statistics mean and standard deviation were calculated, and the independent t-test was conducted to compare continuous variables between the two groups at a 95% confidence interval. A significance level of less than 0.05 was used to consider the results significant.

RESULTS

At the Department of Oral and Maxillofacial Surgery, a prospective randomized comparative study comprised 40 healthy participants with impacted mandibular third molars. The participants ranged from 18 to 41 years, with a mean age of 30 years. Of the total sample, 22 participants were female, and 18 were male, and they were randomly divided into two groups of 20 patients each.

To compare the data related to pain, swelling, and mouth opening, we calculated the mean, standard deviation, and standard error mean for each group and used the paired t-test to determine any statistically significant differences. Our analysis (Table 1,2) and (graph 1) showed statistically significant differences in pain measurements between the Sub mucosal and transdermal patch groups ($P < 0.05$) at the pre-op, and 24th-hour timepoints, but not at the 1st hr, 6th hr, and 7th day ($P = 0.149$), which was statistically insignificant.

TABLE 1: pain scale measurements taken at 1 hour, 6 hours, 24 hours, and 7 days post operation.

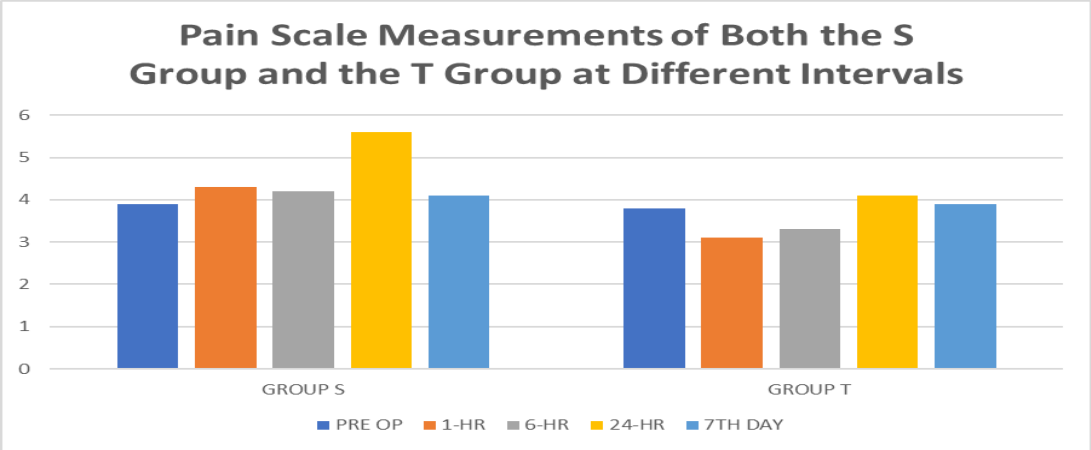
Pain(Vas)Time Timeline	N	Mean		Std. Dev.		Std. Error Mean	
		Group S	Group T	Group S	Group T	Group S	Group T
Pre op	20	3.9	3.8	0.78	0.22	0.34	0.65
1-HR	20	4.3	3.1	1.05	1.28	0.23	0.28
6-HR	20	4.3	3.3	0.87	1.23	0.19	0.27
24-HR	20	5.6	4.1	0.93	0.78	0.2	0.17
7-DAYS	20	4.1	3.9	0.82	0.69	0.18	0.15

The data presented in the table indicates that the pain details of both groups were documented and analyzed using the measures of mean, standard deviation, and standard error mean.

TABLE 2: The Results of a Paired T-Test conducted to analyze the pain data of both groups.

Pain (Vas) Paired T-Test Between Both Groups	T	Df	Sig. (2-Tailed)
Pre op	-3.87	19	.003
group S 1hr - group T 1hr	2.38	19	.008
group S 6hr - group T 6hr	-3.48	19	.03
group S 24hr - group T 24hr	-2.17	19	.004
group S 7th day - group T 7th day	-1.50	19	.149

The table displays the results of a Paired T-Test performed to evaluate the pain levels at 1 hour, 6 hours, 24 hours, and 7 days post-operation.



GRAPH 1: The Pain Scale Measurements of Both the S Group and the T Group at Different Intervals

The graph represents the levels of pain the patients experienced at various time intervals, specifically pre-operation, post-operation at one hour, post-operation at six hours, and post-operation at twenty-four hours and 7th day for both groups.

Our data analyses (Tables 3 and 4) & (Graph 2) revealed statistically significant differences in swelling measurements between the S group & T group ($P < 0.05$) at the pre op time line. However, the 1st hour, sixth- and twenty-fourth-hour follow-up measurements exhibited p-values of 0.19, 0.126, and 0.306 respectively, indicating no statistically significant differences.

TABLE 3: The swelling values for both groups at 1 hour, 6 hours, 24 hours, and 7 days after the procedure.

Swelling At Different Time Inverval	N	Mean		Std. Dev.		Std. Error Mean	
		Group M	Group Y	Group M	Group Y	Group M	Group Y
PRE OP	20	12.8	12.6	1.67	1.21	0.42	0.55
1-HR	20	14.9	15.2	1.76	1.65	0.39	0.37
6-HR	20	15.1	16.3	1.75	1.63	0.39	0.36
24-HR	20	15.6	16.8	1.62	1.61	0.36	0.36

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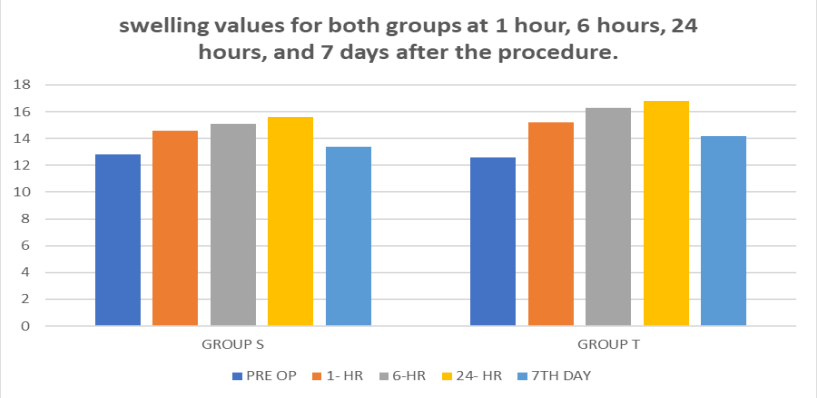
The table displays the mean swelling values observed between the groups, which have been analyzed using statistical measures such as mean, standard deviation and standard error mean.

TABLE 4: The outcomes of a paired T-test swelling values in both M group and Y group

Swelling Paired T-Test Between Both Groups	T	Df	Sig. (2-Tailed)
Group S PRE OP – Group T PRE OP	2.762	19	.002
group M 1hr - group Y 1hr	-2.566	19	.019
group M 6hr - group Y 6hr	-1.600	19	.126
group M 24hr - group Y 24hr	-1.051	19	.306

The table displays the outcomes of a paired T-test conducted to scrutinize the swelling data of both groups at different time intervals, namely post-operation 1st hour, 6th hour, 24th hour, and 7th day.



GRAPH 2: The Swelling Scales Values for the S Group and the T group at Various Time Intervals

The graph illustrates the extent of swelling that patients experienced at different time intervals, namely pre-operation, immediately after the operation, post-operation at six hours, post-operation at 24 hours, and post-operation on the seventh day for both groups.

Our analyses (Tables 5 and 6) & (Graph 3) revealed statistically significant differences in Mouth opening measurements between the both groups ($P < 0.05$) at the 6th hour , 24th hour post-op and seven-day follow-up time points, but pre op and 1st hour shows statistically insignificant.

TABLE 5: The mouth opening values recorded for both groups, which have been analyzed using statistical measures such as mean, standard deviation, and standard error mean.

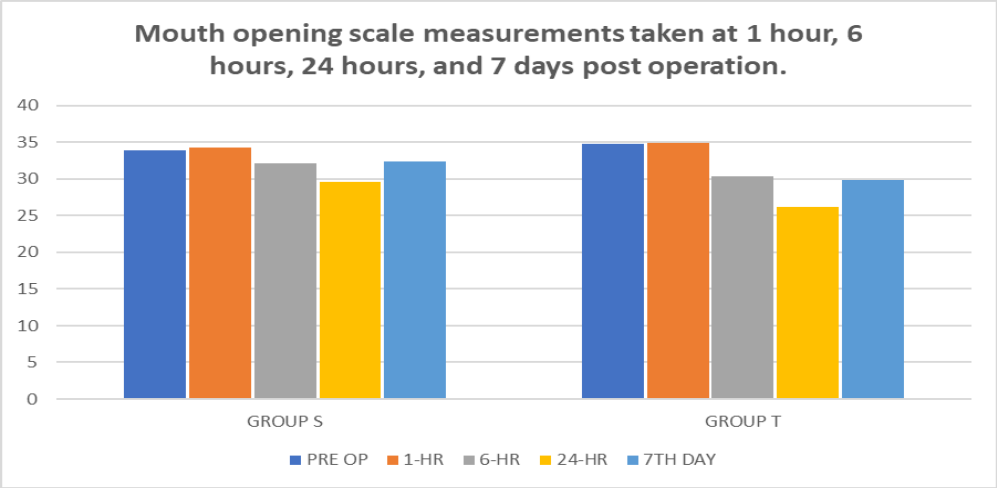
Mouthopening Time Timeline	N	Mean		Std. Dev.		Std. Error Mean	
		Group S	Group T	Group S	Group T	Group S	Group T
Pre op	20	33.9	34.8	0.78	0.22	0.34	0.65
1-HR	20	34.3	34.9	1.05	1.28	0.23	0.28
6-HR	20	32.1	30.4	0.87	1.23	0.19	0.27
24-HR	20	29.6	26.2	0.93	0.78	0.2	0.17
7-DAYS	20	32.4	29.8	0.82	0.69	0.18	0.15

The table displays the mouth opening values recorded for both groups, which have been analyzed at different time points, namely immediate post-operation, 7th day post-operation, and 1-month post-operation.

TABLE 6: The mouth opening outcome Paired T Test values in both M group and Y group

MOUTH OPENING Paired T-Test BETWEEN BOTH GROUPS	t	df	Sig. (2-tailed)
Pre op	-3.83	19	.04
group S 1hr - group T 1hr	2.31	19	.09
group S 6hr - group T 6hr	-3.43	19	.003
group S 24hr - group T 24hr	-2.11	19	.002
group S 7th day - group T 7th day	-1.5	19	.009

This table displays the findings of a paired T-test that was performed to analyze the mouth-opening measurements of two groups at different time intervals, including pre-operation, 1 hour after the operation, 6 hours after the operation, 24 hours after the operation, and on the 7th day after the operation.



GRAPH 3: The Measurements of mouth-opening for Both the S Group and the T Group of Patients

The graph displays the mouth opening measurements at different time intervals, including pre-operation, 1 hour after the operation, 6 hours after the operation, 24 hours after the operation, and on the 7th day after the operation.

DISCUSSION

A comparative analysis was conducted to evaluate the effectiveness of submucosal diclofenac and transdermal patch in managing postoperative pain in patients who underwent third molar surgery. Results indicated that the submucosal administration of diclofenac exhibited a faster onset of action, leading to a more comfortable surgical experience, while the transdermal patch exhibited a slower onset of action but prolonged analgesic effects. Postoperative pain was characterized by localized inflammation and varying degrees of pain due to the release and synthesis of histamine, bradykinin, and prostaglandins caused by tissue and cellular damage during extraction. The study found that the preemptive administration of the drug can prevent severe pain. The manipulation

of soft tissue, the removal of bone, and the duration and intensity of the surgical procedure were contributing factors to the degree of swelling. The mechanism of action of diclofenac involves inhibiting the COX enzymes, thereby reducing the production of prostaglandins and other inflammatory mediators, subsequently reducing swelling and pain. The submucosal administration of diclofenac was effective in reducing swelling and mouth opening after the surgery. The study revealed that statistically significant differences in pain, swelling, and mouth opening were observed between the submucosal and transdermal groups. The results suggest that the submucosal administration of diclofenac is more effective in managing postoperative mouthopening and swelling in third molar surgeries. A Paired T test was conducted to assess the statistical significance of postoperative swelling in both groups. The results showed a statistically significant difference of 0.02 for preoperative measurements, but the remaining timeline was found to be statistically insignificant. Similarly, a Paired T test was conducted to assess the statistical significance of postoperative mouth opening in both groups, and the results showed a statistically significant difference of 0.03 and 0.02 for 6 hours and 24 hours, respectively, while the remaining timeline was statistically insignificant. On the other hand, a statistically significant difference in postoperative pain was observed in both groups, as assessed by the Paired T test, with the results being 0.03 and 0.04 for preoperative, 1 hour, and 24-hour groups. Ramvihari Thota et.al (21) conducted a split-mouth study in which oral diclofenac was administered on one side of the impaction and a transdermal patch was used on the other side after 3 days. Their findings suggest that transdermal diclofenac sodium can serve as an effective alternative for pain relief following the extraction of impacted mandibular third molars. A similar study by Aimuamwosa et. al (22) was conducted with a larger sample size of 68 patients, which was not split-mouth in design. They concluded that transdermal diclofenac sodium can be a viable alternative to oral diclofenac for pain relief in patients who are unable to take the medication orally, particularly in the context of third molar surgery. The appropriateness of using topical NSAIDs for acute pain management is a contentious matter in the field of analgesic practice. While their prescription is prevalent in certain regions, such as Western Europe, they are viewed as being no more effective than a placebo (23) in other parts of the world. Gorecki et al. utilized hydroxypropyl-β-cyclodextrin as a complexing agent to enhance the solubility of Diclofenac sodium. This approach enabled the use of smaller volumes for subcutaneous (SC) or submucosal application, providing an effective means of delivering the drug.

Other studies by Gönül, O et.al (24)conducted on submucosal drugs, including tramadol, and found that submucosal tramadol is a trustworthy, safe, and effective approach to alleviate postoperative acute facial pain after impacted third molar surgery. These advancements (25) in pharmaceutical technology have facilitated the development of a diverse range of diclofenac drug products, intended to alleviate various painful and inflammatory ailments. These improvements in the biopharmaceutical properties of diclofenac have contributed to the evolution of diclofenac products over time. Transdermal patches provide a longer-lasting analgesic effect compared to oral medication, which has a shorter duration of action. The patch gradually releases the drug into the body over a prolonged period, resulting in sustained efficacy and added convenience (as transdermal patches need to be applied only once a day, while oral medication needs to be taken three times a day). In recent decades, transdermal patches have become a popular analgesic modality due to their ease of application, reduced risk of dose dumping compared to creams, constant and prolonged duration of action, self-administration capability, and ease of termination.

LIMITATIONS

The study's findings should be interpreted with caution due to the limited scope of the research, including a small sample size and a narrow range of parameters tested.

CONCLUSION

In conclusion, the use of preemptive analgesics during the early stages of surgery is important to reduce pain and improve outcomes. The submucosal group has a faster onset but shorter duration of action, and is associated with less swelling and improved mouth opening compared to the transdermal patch. The transdermal patch forms delivers slow release of drug into the body over time resulting in long term effectiveness and added convenience. Thus, it seems to be a promising modality carving a niche for the management of pain in the immediate post operative phase. However, additional studies with larger sample sizes are needed to further confirm these findings.

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