Efficacy of a single dose of a transdermal diclofenac patch as pre-emptive postoperative analgesia: a comparison with intramuscular diclofenac

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Abstract

Background: We compared the analgesic efficacy of a transdermal diclofenac patch 100 mg (NuPatch® 100, Zydus Cadila, Ahmedabad, India) and intramuscular diclofenac sodium 75 mg (Voveran®, Novartis, India) for postoperative analgesia, and the associated side-effects of the transdermal diclofenac patch.

Method: Sixty participants in the study were randomly allocated to two groups of 30 each, by a computer-generated randomisation table. The anaesthetic procedure was standardised. A transdermal diclofenac patch 100 mg was applied to the participants in the study group at the beginning of the surgery. In the control group, 75 mg of diclofenac sodium was given intramuscularly half an hour before the end of surgery. Pain was assessed postoperatively at two-, six-, and 12-hour intervals using a visual analogue scale (VAS). An injection of tramadol 2 mg/kg was administered intramuscularly as rescue analgesia. The study ended when the patients asked for rescue analgesia, or when the VAS score was > 5.

Results: The mean duration of analgesia in the control group was 7 hours 28 minutes, and in study group, it was 8 hours 6 minutes, which was comparable (p-value < 0.341).

Conclusion: Intraoperative application of a single dose of 100 mg transdermal diclofenac patch is as effective as a single dose of intramuscular diclofenac (75 mg) for acute postoperative pain, without any significant side-effects.

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Introduction

Peripheral tissue injury, as seen in postoperative patients, provokes two kinds of modification in the responsiveness of the nervous system. In peripheral sensitisation, there is a reduction in the threshold of nociceptive afferent peripheral terminals. In central sensitisation, an activity-dependent increase in the excitability of spinal neurons occurs. This results in an overall hypersensitivity state in the postoperative period. Prevention and establishment of this hypersensitivity state could lead to reduced postoperative pain. This forms the basis of pre-emptive analgesia.[1,2] Non-steroidal anti-inflammatory drugs (NSAIDs) exert anti-inflammatory and analgesic effects through the inhibition of prostaglandin synthesis, by blocking the activity of cyclo-oxygenase. Diclofenac sodium is a commonly used non-selective NSAID, and is available in various forms to treat pain.[3,4] The diclofenac transdermal patch is a newly introduced delivery system for postoperative pain management. This clinical study was undertaken to evaluate the analgesic efficacy of a diclofenac transdermal patch in the postoperative period in patients undergoing lower limb orthopaedic surgery, under subarachnoid block.

Method

After obtaining institutional ethical committee clearance, the study was undertaken in 60 patients aged 18-60 years old of either gender, belonging to American Society of Anesthesiologists (ASA) class I and II, and scheduled for elective lower limb orthopaedic surgery, under subarachnoid block. This followed the attainment of written informed consent. The sample size was calculated using the principal variable, the visual analogue scale (VAS) scores for

postoperative pain, and considering a difference of 2 cm as clinically significant (estimated mean standard deviation 1.5-2.5 cm). The total sample size was calculated as 60 with a type I error of 0.05, and a statistical power of 90%. Patients with clinical features or a history of renal pathology, bronchial asthma, active peptic ulceration, or any other allergic reactions induced by aspirin or other NSAIDs, were excluded. The 60 participants in the study were randomly allocated into two groups of 30, using a computer-generated randomisation table. The study group received a single dose of a transdermal diclofenac patch 100 mg, and the control group received a single dose of intramuscular diclofenac sodium 75 mg. A thorough pre-anaesthetic evaluation was performed by taking the patients' history and by conducting a clinical examination. On the day of the surgery, an 18-gauge intravenous line was secured, and the patients were moved to the operating theatre. Routine monitors were attached. All participants were administered subarachnoid block in the lateral position, using 0.5% hyperbaric bupivacaine using a 23- or 25-gauge Quincke's needle to obtain a sensory level block of T6-T8. Both groups did not receive any intravenous analgesics or sedatives during the surgery. A transdermal diclofenac patch containing 100 mg of diclofenac diethylamine (NuPatch® 100, Zydus Cadila, Ahmedabad, India) was applied to participants in the study group at the beginning of the surgery. In the control group, 75 mg of diclofenac sodium (Voveran®, Novartis, India) was given intramuscularly half-an-hour before the end of surgery. Pain was assessed postoperatively at two, six, and 12 hours using a VAS. At any time during the study, if the VAS was more than, or equal to, five, then an injection of tramadol 2 mg/kg was administered intramuscularly as rescue analgesia, and the study ended. The time at which rescue analgesia was given was noted.

Results

The demographic data with respect to age and gender were comparable between the two groups (Table I).

Table I: Duration of surgery

Groups	Mean	Standard deviation (minutes)
Control group	1 hour 58 minutes	24.6
Study group	2 hours 10 minutes	27.0

The mean duration of surgery in the control group was 1 hour 58 minutes, ± 24.6 minutes, and in the study group it was 2 hours 10 minutes, ± 27 minutes. The duration of surgery was comparable between the groups (p-value = 0.2295), and was not significant. The level of blockade obtained was also comparable between the two groups.

Pain was assessed postoperatively using VAS at two and six hours (Table II). If the patient had a VAS score of < 5, or did not ask for rescue analgesia, a further assessment was carried out at 12 hours. If the patient had a score of ≥ 5 or more, rescue analgesia, in the form of an injection of tramadol 2 mg/kg was given, and the study ended.

Table II: Visual analogue scale pain score in the control group

VAS	2 hours	6 hours
0	29	4
1	0	1
2	1	13
3	0	9
4	0	2
5	0	1

In the control group, at two hours postoperatively, 29 of the 30 patients had no pain and one patient had a VAS score of 2 (Figure 1). At six hours postoperatively, one patient asked for rescue analgesics, whereas four patients had a VAS of 0, 13 patients had VAS of 2, and nine patients had a VAS of 3. All of the remaining patients received rescue analgesia between the 6- and the 12-hour period. The mean time at which rescue analgesia was administered in the control group was 7 hours 28 minutes, with a standard deviation of 1 hour 4 minutes. This result shows that the duration of analgesia provided by intramuscular diclofenac is short. Because patients had already received rescue analgesia, the VAS scores at the 12- and 24-hour times had no significance.

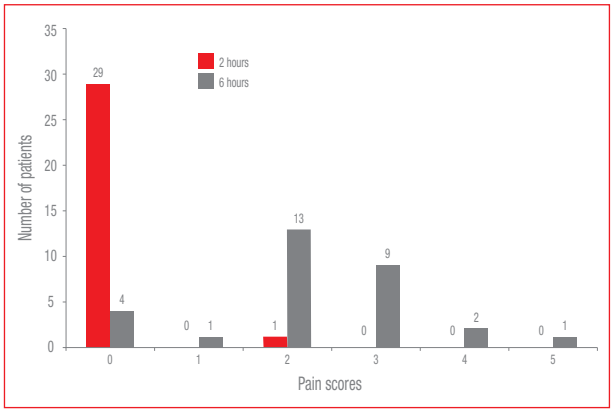

Figure 1: Pain scores in the control group

In the study group, at two hours, 29 patients had no pain, and one patient had a pain score of 2 (Table III). At the end of six hours, seven patients had no pain, and 15 had a score of 2, whereas three patients had a score of 5. At 12 hours, only one patient had a score of 4, and the others had received rescue analgesia (Figure 2).

Table III: Pain scores in the study group

Score	Time (hours)		
	2 hours	6 hours	12 hours
0	29	7	0
1	0	2	0
2	1	15	0
3	0	3	0
4	0	0	1
5	0	3	0

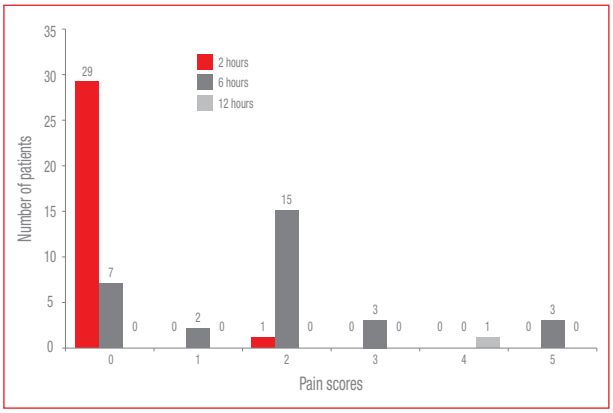

Figure 2: Pain scores in the study group

At two hours postoperatively, the VAS was comparable between the groups, and was not statistically significant (p-value = 1). At six hours postoperatively when the VAS was compared between the two groups using chi-square tests, the results were comparable. At 12 hours postoperatively, only one patient in the study group had a score of 4 without rescue analgesic.

The mean time at which rescue analgesia was given in the control group was 7 hours 28 minutes ± 1 hour 4 minutes, and in study group, it was 8 hours 6 minutes ± 2 hours (Table IV). Both the groups were comparable, and when analysed using an unpaired t-test, they were found to be not significant (p-value 0.34).

Table IV: Time at which rescue analgesia was given, and the amount

Groups	Time at which rescue analgesia was requested Mean ± standard deviation
Control group	7 hours 28 minutes ± 1 hour 4 minutes
Study group	8 hours 6 minutes ± 2 hours

Side-effects in patients receiving intramuscular diclofenac included abdominal pain (gastritis) in three patients, and pain at the injection site in two patients. Two patients developed erythema at the site where the patch was applied in the study group. When the side-effects were compared between the groups using a test of proportions, it was not significant.

Discussion

The results of our study suggest that when applied at the beginning of surgery, a transdermal patch of diclofenac is as effective as intramuscular diclofenac in prolonging the requirement of postoperative opioids. The transdermal drug delivery offers several advantages as it avoids the need for intravenous or intramuscular drug administration, and is an option in patients who are unable to swallow oral medications. Transdermal drug administration also bypasses first-pass metabolism in the liver, and overcomes concerns regarding drugs that are poorly absorbed in the gastrointestinal tract. An important concern with regard to transdermal drugs is the prolonged duration of onset and offset, typically 12-24 hours[5] unlike intravenous or intramuscular medications, which can be used as needed for pain control or nausea. Use of a transdermal agent requires planning and careful timing. In the postoperative setting, these agents are applied in anticipation of pain, and not after the patient experiences pain. This is due to the long onset duration. Topical NSAIDs may have potential advantages when compared with oral NSAIDs. Neadal demonstrated that because of low systemic concentrations, topical NSAIDs have a reduced risk of upper gastrointestinal complications, such as gastric and peptic ulcers, and gastrointestinal nuisance symptoms, such as dyspepsia.[6] Parenteral drug delivery with intravenous, subcutaneous, or intramuscular injection, can gain easy access to systemic circulation with rapid drug absorption. Unfortunately, this rapid drug absorption is also accompanied by a rapid decline in the drug levels in the systemic circulation.[7]

Although opioids are effective analgesics with no analgesic effect ceiling, their efficacy is often limited by their tolerability profile. Currently, regimens consisting of a combination of analgesics (multimodal analgesia) are recommended for the management of postoperative pain. Adjunctive techniques, such as wound infiltration with local anaesthetics, the use of NSAIDs or corticosteroids, and epidural administration of opioids, have been recommended to treat postoperative pain.[1,2] Of these, the NSAIDs have gained increasing popularity in treating postoperative pain. NSAIDs are excellent analgesics, with no clinically important difference in efficacy among specific drugs. Side-effects to note include gastrointestinal bleeding, renal dysfunction, and platelet dysfunction.

The mean duration of surgery was comparable between the two groups. The duration of surgery has a bearing on the postoperative analgesic requirement, as prolonged duration of tissue handling increases the local production of inflammatory substances and oedema, hence increasing the requirement for analgesics.

In this study, pain was assessed postoperatively at two, six, 12 and 24 hours using a VAS score, and a VAS score of 5 was considered to represent the need for additional analgesics or rescue analgesics. We used an injection of tramadol 2 mg/kg as a rescue analgesic, and the study was terminated, after which no further assessment was conducted. In the control group, at two hours postoperatively, 29 of the 30 patients had no pain, and one patient had a VAS score of 2. At six hours postoperatively, one patient asked for rescue analgesics, whereas four patients had a VAS of 0, and 13 patients had a VAS score of 2. The mean time at which rescue analgesia was administered in the control group was 7 hours 28 minutes, with a standard deviation of 1 hour 4 minutes.

In a study by Alessandri et al, the authors noted that the rate of discharge in patients receiving a transdermal diclofenac patch with a standard analgesic was comparable to a standard analgesic alone in patients undergoing laparoscopic benign gynecologic surgery.[8] Side-effects encountered in patients receiving intramuscular diclofenac were abdominal pain in three patients, and pain at the injection site in two patients. There were no significant side-effects in patients who received the transdermal diclofenac patch, except for two who had erythema at the application site.[9] Topical and transdermal preparations are associated with a lower incidence of systemic side-effects because of the lower plasma concentration achieved by this modes.[8,10,11]

Pradel et al used a diclofenac patch for acute traumatic blunt soft tissue injuries, and they found that the diclofenac patch was effective and well tolerated. The most frequently observed adverse events were local tissue reactions, such as pruritus and a rash of minor severity.[12]

The safety profile of diclofenac patches has also been emphasised by Mason et al[10] in their systematic review of the use of topical NSAIDs in the UK, and by studies reporting the use of a diclofenac transdermal patch in osteoarthritis[13] and in sports-related injuries.[12]

The problem that we faced during the study was the poor adhesiveness of the transdermal patch. The patch would loosen and peel off when applied to mobile parts of body, such as the arms or the gluteal region. Rather, the transdermal patch needs to be applied to the anterior chest wall or the abdomen.

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