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Original Research Article

Comparison of Postoperative Analgesia between Two Pharmaceutical Forms of Diclofenac (Transdermal Patch versus Intravenous) for Patients Undergoing Inguinal Hernioplasty: A Randomized Control Study

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Abstract:

Background: Perioperative pain control is an important factor since it affects the patient's postoperative morbidity and outcome. Early mobilisation and discharge are facilitated by optimal pain management. Since oral drugs are not allowed in the early postoperative period, injectable analgesia is the most often used painkiller. With a better understanding of the pathophysiology of pain and newer drug delivery methods, efforts are being made to provide patients with adequate pain relief while maximising drug action and minimising systemic side effects, so that when the drug is administered in a suitable way, the patient is also comfortable with it.

Methods: To compare the analgesic effects of diclofenac transdermal patch 100 mg and diclofenac intravenous 75 mg, we conducted a study on 50 patients with ASA I and II grades, ranging in age from 21 to 70 years, and of either gender. Using a computer-generated random number table, the participants were randomly split into 2 groups of 25 each: the group receiving a transdermal patch received a diclofenac patch; the group receiving an intravenous injection received an intravenous injection of diclofenac. By comparing the VAS score and hemodynamic response to pain in both research groups, the length of postoperative analgesia was determined. Both research groups' total number of rescue analgesia prescriptions and their duration were documented. When a patient's VAS score was higher than 3 in the first 24 hours, injection tramadol 2 mg/kg was administered. After administering the study medicines, adverse symptoms such as nausea, gastroenteritis, vomiting, erythema, and pruritis were seen.

Results: Over time, the mean VAS change was similar across the two groups (p-value> 0.05). It was also determined that the two groups' patterns of change were comparable (P value > 0.05). Effective analgesia might be achieved with either the diclofenac patch or intravenous The diclofenac patch resulted in a higher pain score 12 hours after surgery, compared to the intravenous. The duration in the patch group was longer than in the intravenous group ($p < 0.05$). There were fewer systemic adverse effects and fewer signs of local irritation with transdermal patch administration compared to intramuscular injection.

Conclusions: It was concluded that Transdermal diclofenac patch (100 mg) is a better analgesic route than intravenous diclofenac (75 mg) for pre-emptive analgesia in patients undergoing inguinal hernioplasty.

Keywords: Diclofenac, Intravenous injection, Pre-emptive analgesia, Transdermal patch.

Introduction

Postoperative pain is a prevalent issue following any type of surgical surgery and requires effective analgesia. There is a wide variety of global (e.g., personality, age, gender, surgical technique, pre-existing pain syndrome, hereditary) and particular (e.g., rage, anxiety, sadness, fear, psychological) elements that might affect the differential reaction to the tissue injury during surgical incision. [1] When cells are injured or inflamed, they produce chemicals called prostaglandins and other chemical mediators, which excite sensory nerve endings called nociceptors, causing a painful localised feeling. [2] One of the most significant concerns facing modern society and the medical community is the treatment of pain. The inability to function normally due to pain is not only a huge health issue but also a significant economic burden. [2,3] The time after surgery is a crucial aspect of every surgical procedure. Allowing a patient to endure postoperative discomfort is like putting salt in a wound if surgery is an injury. However, postoperative pain is not just the result of tissue injury but also of other neurophysiological interactions, so its effective management is just as

crucial as that of intraoperative pain. [4] Because of this, implementing an effective pain management regimen after surgery is more challenging than it should be. Damage to peripheral tissues causes two distinct shifts in nervous system reactivity. [5,6] There are two types of sensitizations: peripheral and central. In peripheral sensitization, nociceptive afferent terminals in the periphery have their threshold lowered. Spinal nerves become more excitable in response to activity, a process known as central sensitization. [7]

The inguinal hernia accounts for around 75% of all hernias in the abdominal wall and is thus the most frequent kind of hernia worldwide. Inguinal hernias can be treated with a variety of surgeries, most of which have a low risk of recurrence and complications, although postoperative discomfort remains a serious issue. [8] This causes postoperative hypersensitivity. Reduced postoperative pain may result from efforts to both prevent and establish this hypersensitivity. This laid the groundwork for pre-emptive analgesic issues that might lengthen a patient's stay in the hospital and prevent them from walking around on their own.

In addition to traditional painkillers like morphine and nonsteroidal anti-inflammatory medications (NSAIDs) like diclofenac, fentanyl is often prescribed to patients experiencing severe pain after surgery. [9] While oral administration is often preferred in clinical settings, this may not be feasible in the pre- and post-operative periods due to the patient's incapacity to swallow the medication or excessive first-pass metabolism. [3] The parenteral form of this drug is extremely irritating and unpleasant when administered. One relatively new method of treating pain after surgery is with transdermal patches. [10] In addition to diclofenac, these patches can also be used to provide other Nonsteroidal anti-inflammatory drugs. It is given only once a day and is administered without any discomfort or risk to the patient. When compared to intravenous (I/V) medication administration, the prolonged release and reduced plasma concentrations offered by these patches are obvious benefits. [5]

The purpose of this study was to evaluate the efficacy of postoperative diclofenac administration through transdermal patch versus intravenous route in patients following inguinal hernioplasty.

Materials and Methods

Source of Data

This randomized comparative study was conducted for a period of one year from March 2022 to March 2023 at the Department of General Surgery at Indira Gandhi Institute of Medical Sciences (IGIMS), Patna.

Sample size

This research compared the analgesic efficacy of diclofenac transdermal patch 100 mg to that of diclofenac intravenous 75 mg in 50 patients divided into two groups of 25 each scheduled for elective inguinal hernioplasty under spinal anaesthesia. The variance between the two samples was used to determine the necessary sample size.

Inclusion criteria

- Inguinal hernia operations are recommended for ASA I and II patients between the ages of 21-70 years of either gender.
- Patients' hemodynamics are stable, all diagnostic tests are within normal ranges, and they have no additional medical conditions.

Exclusion criteria:

- Patients having a physical condition of ASA III or above.
- Patients suffering from many conditions at once, such as diabetes, hypertension, neurological, mental, or neurovascular illness.
- Patients exhibiting drug refusal or allergy symptoms.

Methodology

Prior to starting the study, clearance from the institutional ethical committee was obtained. Following strict inclusion and exclusion criteria, 50 patients receiving spinal anaesthesia for inguinal hernioplasty operations were randomly chosen and split into two groups of 25 using a computer-generated random number table.

Transdermal patch: Diclofenac patch of 100 mg.

Intravenous: Diclofenac 75mg.

On the day before the procedure, the preoperative assessment was completed, and a thorough history and list of complaints were made. The circulatory, pulmonary, and central nervous systems will be thoroughly and generally examined. Hemograms, liver function tests, renal function tests, serum electrolytes, urine routines, bleeding time and clotting time (BT-CT) tests, among other normal laboratory investigations, were performed. Before surgery, patients were instructed to fast starting at midnight. An informed written consent was obtained.

Preoperative measurements included heart rate (HR), systolic and diastolic blood pressures (SBP, DBP), mean arterial pressure (MAP), electrocardiogram (ECG), and oxygen saturation (SPO2). For the purpose of preloading the patient with 10ml/kg of Ringer's lactate, peripheral venous access was obtained using a 20G IV cannula.

All monitors, including an ECG, pulse oximeter, and NIBP, were attached when I arrived at the

operation theatre. The consultant anesthesiologist performed a lumbar puncture using a 26G Quincke's spinal needle at levels L3-L4 while the patient was in the sitting position and under aseptic conditions. 3.5ml of Bupivicaine 0.5% heavy was then injected after the needle tip was confirmed to be in the subarachnoid space by a free and clear flow of CSF. After spinal anaesthesia, the patient was made to lie in a supine position. Diclofenac patch (100 mg) was applied to the lateral aspect of the contralateral thigh in group patients after confirming an adequate level of sensory blockade (T10, at level of umbilicus), and diclofenac intravenous (75 mg) was administered in the contralateral gluteal region in group patients prior to surgery.

After surgery, patients' levels of discomfort were measured on a VAS and VRS at 1, 2, 4, 6, 8, 12, and 24 hours. Tramadol 2 mg/kg was injected as a rescue analgesic if the VAS was greater than 5 or the VRS greater than 1 at any moment during the research. Rescue analgesia administration times were recorded. Pruritis, vomiting, and nausea were reported as side effects.

Statistical analysis

In order to produce a master chart, the data was input into Microsoft Excel. A statistical software for SPSS version 20 was then used to load the master chart for additional statistical analysis. The master graphic contained both qualitative and quantitative information. The analysis included both descriptive and inferential statistics. Frequency and percentages were employed to describe qualitative factors. The terms mean and standard deviation were employed to describe the quantitative data. Independent samples were tested to determine the mean difference between the two groups. The Repeated Measures Analysis of Variance (RM-ANOVA) was employed to determine the difference in mean change between the groups for variables that were repeatedly assessed. Statistical significance was defined as a p-value less than 0.05.

Results

In all, about 50 patients receiving spinal anaesthesia for inguinal hernioplasty operations, who met the inclusion criteria were included in the prospective study. This study looked at potential risk variables such as gender, age, ASA grade, measured on a VAS and VRS, side effects and other characteristics were compared statistically in both groups like Transdermal patch vs Intravenous.

Demographic details of patients

The patients were split with respect to ASA grade was comparable between the 2 groups; Transdermal Patch had 19-ASA I and 6-ASA II patients; Intravenous had 17-ASA I and 8-ASA II patients (Table-1).

The distribution of ASA I in the Transdermal Patch was higher than Intravenous with p-value> 0.05, which was statistically insignificant.

Table 1: ASA grading

ASA Grade	Transdermal Patch		Intravenous	
	N	%	N	%
I	19	76	17	68
II	6	24	8	32
Total	25	100	25	100

The demographic data with respect to gender was comparable between the 2 groups. A total of 14(56%) males and 11(44%) females were prescribed Transdermal Patch, however, 16 (64%) males and 9 (36%) females were put on Intravenous medications (Figure 1A).

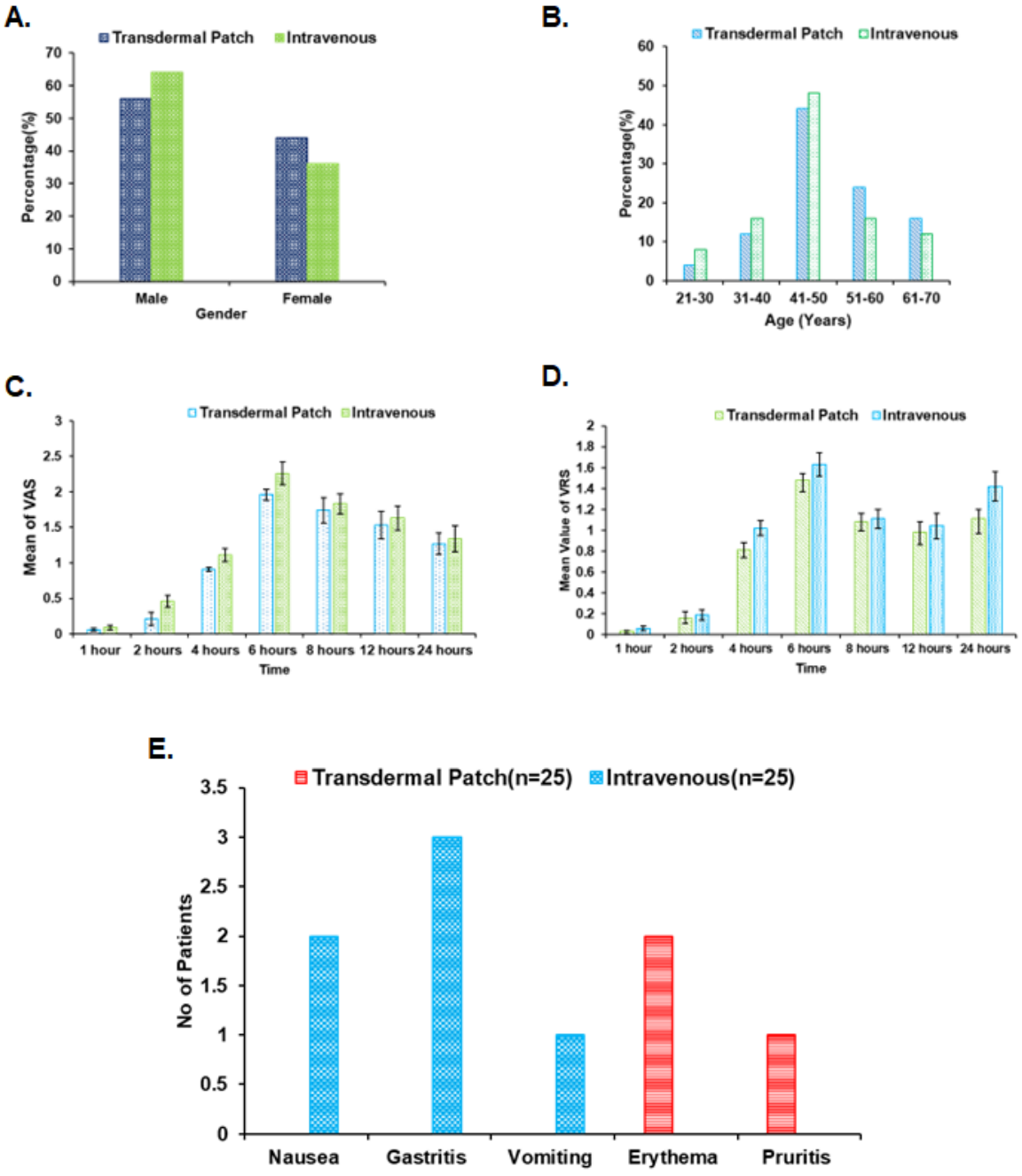

Figure 1: (A) Percentage of Gender Distribution; **(B)** Percentage of Age Distribution; **(C)** VAS score at different time intervals for diclofenac transdermal patch versus intravenous group in postoperative patients of inguinal hernia; **(D)** VRS score at different time intervals for diclofenac transdermal patch versus intravenous group in postoperative patients of inguinal hernia; **(E)** Comparison of the side effects between the two groups diclofenac transdermal patch versus intravenous group.

The patients under Transdermal Patch had an age group ranging from 21-70 years with a mean age of 45.2± 4.38 years, whereas the Intravenous patient's age group varied between 21 and 70 years with a mean age of 46.4±4.71 years.

In the present study, most patients in groups taking Transdermal Patches and Intravenous belonged to adults 41-50 years age groups (44% vs. 48%), followed by old patients 51-70 years (40% vs. 28%) and the least number of patients belonged to 21-40 years (16% vs. 24%) was shown in Figure-1B

In Transdermal Patches, the mean VAS score was 0.06 ± 0.02, 0.21 ± 0.09, 0.91 ± 0.03, 1.96 ± 0.08, 1.74 ± 0.18, 1.53 ± 0.19, 1.27 ± 0.15 at 1, 2, 4, 6, 8,12 and 24 hours respectively, while in Intravenous the mean VAS score was 0.09 ± 0.03, 0.46 ± 0.0 8, 1.11 ± 0.09, 2.26 ± 0.16, 1.83 ± 0.14,

1.63 ± 0.17, 1.34 ± 0.18 at 1, 2, 4, 6, 8, 12 and 24 hours respectively (Table 2& Figure 1C).

Table 2: Comparison of Visual Analogue Score (VAS)

Variable	Transdermal Patch (n=25)		Intravenous (n=25)		P value	
	Mean	SD	Mean	SD	Within	Between
1 hour	0.06	0.02	0.09	0.03	0.632	0.112
2 hours	0.21	0.09	0.46	0.08		
4 hours	0.91	0.03	1.11	0.09		
6 hours	1.96	0.08	2.26	0.16		
8 hours	1.74	0.18	1.83	0.14		
12 hours	1.53	0.19	1.63	0.17		
24 hours	1.27	0.15	1.34	0.18		

The mean change in VAS was similar over the timeline in both the groups with p-value of 0.632, which was > 0.05 and was statistically insignificant.

However, in the intergroup comparison in both groups, the change in mean VAS was similar over the timeline in both the groups with a p-value of 0.112, which was > 0.05 and was statistically insignificant.

The mean pain score as assessed by VRS score in the transdermal patch group was 0.03±0.01, 0.16±0.06, 0.81±0.07, 1.48±0.06, 1.08±0.08, 0.98±0.1 and 1.11±0.09 at 1, 2, 4, 6, 8, 12, and 24 hours respectively. While the mean VRS score for the Intravenous group was 0.06±0.02, 0.19±0.05, 1.02±0.07, 1.63±0.11, 1.11±0.09, 1.04±0.12 and 1.42±0.14 at 1, 2, 4, 6, 8, 12, and 24 hours, respectively. Similarly, the analgesic effect reflected by verbal rating scale (VRS) scores was also at a mild intensity, but at 24 hours of the postoperative period, a significant statistical difference was observed in the mean scores between the two groups (Table 3 & Figure 1D).

Table 3: Comparison of Visual Rescue Score (VRS)

Variable	Transdermal Patch (n=25)		Intravenous (n=25)		P value	
	Mean	SD	Mean	SD	With in	Between
1 hour	0.03	0.01	0.06	0.02	1.132	0.046
2 hours	0.16	0.06	0.19	0.05		
4 hours	0.81	0.07	1.02	0.07		
6 hours	1.48	0.06	1.63	0.11		
8 hours	1.08	0.08	1.11	0.09		
12 hours	0.98	0.1	1.04	0.12		
24 hours	1.11	0.09	1.42	0.14		

Table 4 and Figure 1E show the comparison of the side effects between the two groups. In the transdermal patch group, out of 25 patients, 2 patients (8%) had complaints of erythema, and 1 patient (4%) had complaints of pruritis. In the Intravenous group, out of 25 patients, 2 patients (8%) had nausea, 3 patients (12%) had gastritis and 1 patient (4%) had vomiting.

Table 4: Comparison of Adverse Effects

Side effects	Transdermal Patch (n=25)	Intravenous (n=25)
Nausea	0	2
Gastritis	0	3
Vomiting	0	1
Erythema	2	0
Pruritis	1	0

Discussion

Nociception, a nervous system activity brought on by nociceptors being stimulated, results in pain, which can have an impact on a person's quality of life and general functioning and is a major sign of many diseases. [8] A medicine known as pre-emptive analgesia is said to be taken before surgery in order to prevent the onset of central sensitization, which is brought on by incisions and results in inflammatory damage that occurs both during surgery and in the immediate postoperative period. [11]

Pre-emptive analgesia is more successful than a similar analgesic therapy initiated after surgery because of this "protective" impact on the nociceptive system. It also lessens the emergence of chronic pain by altering the central sensory

processing induced by inflammatory and incisional injuries. [12, 13]

Opioid and non-opioid drug classes are generally used to treat postoperative pain. [14] Opioid analgesics are by far the most significant class of medications and continue to be the cornerstone of postoperative pain management. Although opioid postoperative analgesics are effective, their effectiveness is frequently constrained by the onset of tolerance, physical dependency, possible risks of over sedation, and respiratory depression. [15] NSAIDs, particularly diclofenac, have grown in popularity among non-opioid medications for managing postoperative pain. [16] However, diclofenac is likewise accompanied by boxed warnings and has its own side effects whether used parenterally or orally. Currently, multimodal analgesia—a mix of analgesics—is advised for the treatment of postoperative pain. [17] Diclofenac is a common NSAID that anesthesiologists use for postoperative analgesia. [18] They lessen postoperative pain either on its own or in conjunction with opioids. Additionally, the opioids sparing effect of NSAIDs can sometimes result in a reduction of the need for opioids of up to one third. NSAIDs can be used topically and have been shown to reduce both acute and chronic pain. [19] The transdermal patch, a recent advancement in drug delivery technology, has many benefits including painless drug administration, increased bioavailability, maintenance of constant and prolonged drug levels, decreased frequency of dosing, minimization of inter- and intra-patient variability, ease of self-administration, and ease of medication discontinuation, all of which improve patient compliance. It also provides a wonderful alternative for people who are unable to take medications orally. Transdermal drug delivery also allays worries about medications that are poorly absorbed in the gastrointestinal route since it avoids first-pass liver metabolism. [20]

We conducted a prospective, comparative, randomised study with 50 patients in the ASA I and II grades, ranging in age from 21 to 70 years, of either gender, in order to compare the effectiveness of transdermally applied diclofenac patch 100 mg versus intravenously administered diclofenac. This was done in order to better understand the significance of perioperative pain management.

25 patients were chosen for each group after the inclusion and exclusion criteria were taken into account. Regarding gender, age, and the distribution of ASA-grades, there were no statistically significant variations between the patients in the two groups.

In our study, postoperative pain was measured by VAS and VRS ratings at 1, 2, 4, 6, 8, and 24 hours. For supplementary or rescue analgesics, a VAS score of more than 5 and a VRS score of more than 2 were deemed necessary. As a last-resort painkiller, injection tramadol 50 mg i.v. was made accessible. However, giving diclofenac intravenously to inguinal hernia postoperative patients led to a noticeable analgesic effect throughout the postoperative period, including at 1, 2, 4, 6, 8, and 12 hours. The analgesic effect of diclofenac transdermal patch was similar to that of diclofenac intravenous, and the degree of pain was consistently kept at a modest level during the observation period. At 6, 8, 12, and 24 hours, none of the patients in the group transdermal patch had any rescue medication, though. Even though the two groups' mean VAS score changes over time were comparable, there were substantially more patients in the intravenous group who needed rescue analgesia than in the transdermal patch group. Although the group transdermal patch experienced discomfort more quickly, just a little amount of rescue medication was needed over the course of 24 hours.

Our findings are consistent with research findings that other scientists have noted. Dinesh Govinda Rao, et al. [21] compared the intramuscular diclofenac injection (75 mg) with the transdermal diclofenac patch (100 mg) as a preventative analgesic in delivering post-operative analgesia in Hernia repair procedures. Just after spinal anaesthesia, as in our trial, the study medicines were given to the study groups. At 2, 6, and 12 hours after surgery, the VAS (Visual Analogue Scale) was used to evaluate the postoperative analgesia. At 4 hours, they did not measure pain, nevertheless. In this trial, the average time of postoperative analgesia was 8.9 2.16 hours for the DI group and 10.28 2.54 hours for the diclofenac patch group. This was different from our study since the mean duration of postoperative analgesia in our study's group DP was 4 hours whereas it was 6 hours in the group receiving a diclofenac injection. Additionally, the VAS score at which the rescue medication was administered in their trial was 8, whereas it was VAS score 3 in our study.

Gopal Swaroop Bhargava, et al. [22] examined the effectiveness, duration, and quality of analgesia on the visual analogue scale as well as the adverse effects of diclofenac transdermal patch (100 mg) with diclofenac intramuscular injection (75 mg) for postoperative pain treatment. When pain was measured using the VAS, it was shown that 8 hours produced the highest pain levels in both groups. In the patch group, the first rescue dosage was required on average after 7.21 hours, whereas it took 7.43 hours in the injection group. Calculated p value was 0.128, which was not significant. In compared to our investigation, the observations also shown variability. In contrast to our study, where study medicines were given immediately

following the induction of spinal anaesthesia, it was found that the study drugs were delivered in that study 1 hour before to the conclusion of the surgery. In contrast to our trial, the administration of rescue medications was done at a VAS score of 5. As a result, the time between a drug's beginning of action and its peak impact might differ.

As preventative analgesia for patients having inguinal hernia operations, Manish Banjare et al. [10] evaluated the efficacy and safety of a diclofenac transdermal patch to intramuscular diclofenac injection. Using a mean VAS score, they found a statistically significant difference in the analgesic effect between the two groups. The average VAS score for those who used a transdermal diclofenac patch grew steadily over the course of 8 hours, rising from a low value at 2 hours. The intramuscular diclofenac injection group had comparable tendencies. At 8 hours, there was a statistically significant difference between the injection group and the patch group in terms of VAS score (p= 0.00). Furthermore, there was a statistically significant difference between the two groups in terms of the amount of time until rescue analgesia was needed after receiving patch vs receiving an injection for pain. Our study varies from this one in that spinal anaesthesia was provided after the study medicines had already been given to the study groups. Moreover, rescue medications were administered to their patients at a VAS score of 5, while in our trial, rescue medication was administered at a VAS level of 3.

In order to determine the best time to administer pre-emptive analgesia, it is necessary to take into account the time of drug administration, its onset, and its peak plasma concentration. This is because the time required to induce anaesthesia and the overall length of surgery may differ depending on the circumstances. The lack of this data in our study restricts our ability to comprehend and contrast the mean duration of analgesia for the study medicines with important variations in the observation.

Additionally, because it is a subjective method of measuring pain, the VAS score cannot be reliable. [23] Safety investigations turned out no obvious major negative consequences. With just two modest incidences of erythema and one case of pruritis, the diclofenac patch was well tolerated. In contrast to prior trials where application site skin responses were often recorded, none of the volunteers had experienced any skin reactions. Two incidences of nausea, three cases of gastroenteritis, and further isolated episodes of vomiting were noted in the diclofenac intravenous treatment group. The transdermal patch's poor adhesiveness was also noted during the trial; the patch would come off when people slept. Consequently, regular checking was required. Applying the patch over the body portion that cannot be moved, such as the chest or abdomen, rather than the arm, maybe a better solution. [8] According to the findings of our study, a transdermal diclofenac patch containing 100 mg reduced postoperative pain in patients with inguinal hernias when applied three hours prior to surgery. Based on our observations, the timely application of a transdermal diclofenac patch to postoperative patients with inguinal hernias can be regarded as a safe and effective method of pain management. The VAS and VRS scores from the diclofenac patch group, however, showed differences in scores when compared to diclofenac intravenously, despite the fact that the scores from both groups were mildly intense throughout the observational period. This was especially true at 24 hours, when a significant difference was seen both clinically and statistically.

Conclusion

Although the diclofenac patch's peak plasma concentration is not reached as quickly as it is with the diclofenac intravenous, the patch has many benefits over intravenous dosing, including being easier to apply and remove, causing fewer local side effects, and having no systemic side effects; it also avoids the first pass metabolism that occurs in the liver, making it suitable for use in patients who are nil per oral postoperatively and in those who complain of nausea or vomiting. So, the patient's cooperation improves. It's preferable since it reduces the need for rescue medicines postoperatively and has a longer duration of effect due to the slow and consistent release of pharmaceuticals. The results of this study suggest that patients having inguinal hernia repair procedures under spinal anaesthesia block may benefit from receiving a transdermal patch (100 mg) as a pre-emptive painkiller before surgery.

Ethical approval: This study was approved, and Institutional Ethics Committee, IGIMS, Patna, Bihar, India, have recommended the decision [Letter No.: 496/ IEC/IGIMS/2022].

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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