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To evaluate efficacy and safety of diclofenac transdermal patch with intramuscular diclofenac injection as preemptive analgesia in post operative patients undergoing inguinal hernioplasty

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ABSTRACT

Context: To evaluate efficacy and safety of diclofenac transdermal patch with intramuscular diclofenac injection as preemptive analgesia in post operative patients undergoing inguinal hernioplasty.
Aims: We aim to compare the duration and quality of analgesia provided by diclofenac trans dermal patch and intramuscular injection and to estimate time at which patients demand rescue analgesia after surgery.
Settings Design: This randomized comparative study was conducted at a tertiary care hospital in central India.
Materials and Methods: 60 healthy patients divided into two groups of 30 each, scheduled for elective inguinal hernioplasty under subarachnoid block were taken. Sample size calculation was based on the difference of means of two independent samples. A transdermal diclofenac patch containing 100 mg of diclofenac diethylamine was applied to the participants in the study group just before the induction of anesthesia. In the control group, 75 mg of diclofenac sodium Inj. was given intramuscularly half-an-hour before the end of surgery.
Data for postoperative pain was assessed at 2, 4, 6, 8, 12, 16 and 24 hours by using a visual analogue scale (VAS) score and verbal rating scale (VRS) score and analysed using upaired t test.
Results: Statistical difference in duration, quality of pre-emptive analgesia and Significant time of rescue analgesia was found between the two groups in terms of postoperative pain in patients undergoing inguinal hernioplasty.
Conclusion: Tran dermal diclofenac patch (100 mg) is a better analgesic route than intramuscular diclofenac sodium (75 mg) for pre-emptive analgesia in patients undergoing inguinal hernioplasty.

1. Introduction

The common problem of any surgical intervention is postoperative pain, and it requires appropriate analgesia. The differential response to the tissue injury during surgical incision can be influenced by many variables including global (i.e. personality, age, gender, surgical approach, preexisting pain syndrome, genetic) and specific (i.e. anger, anxiety, depression, fear, psychological factors).[1]

In postoperative period, due to tissue injury, the responsiveness of the patient's nervous system develops two kinds of modification (a) Peripheral sensitization in which the threshold of the peripheral terminal of the afferent nociceptive is reduced; (b) central sensitization, in which excitability of spinal neurons is increased and develops neuroplasticity. The combined effect of these changes results in a state of hypersensitivity in post-operative period resulting in increased intensity and duration of pain after surgery. This forms the basis of pre-emptive analgesia.[2,3]

Inguinal hernia is the most common type of hernia globally representing approximately 75% of all abdominal wall hernia.[4–6]There are many surgical procedures developed to treat the inguinal hernia which have low rate of recurrence and complications, but postoperative pain is an important

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complication that can delay the ambulation and prolonged hospital stay of patients.

NSAIDs like diclofenac and Opioids like morphine, fentanyl are commonly used to treat post-operative pain.[7] In daily practice oral administration is a route of choice but it is impractical to use this route before and after surgery because of the inability of the patient to take it in some cases and due to high first-pass metabolism. Its parenteral preparation is very painful and irritating at the site of administration. Trans dermal patches are recently introduced drug delivery system for postoperative pain management. These patches are an innovative topical drug delivery system for diclofenac as well as other NSAIDs. Its administration is also very simple, noninvasive and only once in 24 hours.[8] These patches have an advantage over I/V or I/M drug, that is of sustained delivery of drug with lesser systemic side effects due to lower plasma concentrations.[9–11]

We conducted this study to compare intramuscular and transdermal mode of application of diclofenac in patients undergoing inguinal hernioplasty (being a commonly performed surgical procedure) for postoperative analgesia.

2. Materials and Methods

This randomized comparative study was conducted for a period of one year from June 2018 to June 2019 at department of anaesthesiology M.G.M Medical and M.Y.Hospital Indore.

2.1. Sample size

The study was comprised of 60 patients divided into two groups of 30 each scheduled for elective inguinal hernioplasty under subarachnoid block. Sample size calculation was based on the difference of means of two independent samples.

2.2. Inclusion criteria

1. American Society of Anaesthesiologists (ASA) physical status I–II.
2. Age from 18 to 50 years of either gender.

2.3. Exclusion criteria

1. Patient refusal.
2. American society of anaesthesiologist (ASA) status lll-lV.
3. Patients with hypersensitivity reaction to the study drug.
4. Patients with severe hepatic and renal disorders and other co-morbid conditions like Diabetes, Tuberculosis, HIV, etc.
5. Pregnant or lactating women.
6. Gastrointestinal tract related problems (bleeding, perforation and ulcer etc).

2.4. Randomization

Patients were randomly allocated by computer generated random tables to one of the two groups comprising 30 patients each.

2.5. Procedure

After obtaining written informed consent and recording vitals and nill by mouth status as per institutional protocol, all patients were started intravenous fluids. Routine monitors were attached (pulse oximeter for SpO2, heart rate (HR), non-invasive blood pressure, respiratory rate and ECG). All patients were administered subarachnoid block in the sitting position in L3-L4 intervertebral space using 0.5% hyperbaric bupivacaine inj. using a 25-gauge quincke's needle under all aseptic precautions, to obtain a sensory block up to T10 level. Both groups did not receive any intravenous analgesics or sedatives during the surgery.

A transdermal diclofenac patch containing 100 mg of diclofenac diethyl amine was applied to the participants in the study group just before the induction of anesthesia. In the control group, 75 mg of diclofenac sodium Inj. was given intramuscularly half-an-hour before the end of surgery.

2.6. Assessment of postoperative pain and management

Pain was assessed postoperatively at 2, 4, 6, 8, 12, 16 and 24 hours by using a visual analogue scale (VAS) score and verbal rating scale (VRS) score. At any time during the study, if the VAS was more than 5 or VRS more than 1 then an injection of tramadol 2 mg/kg was administered as rescue analgesia and the study ended. The time at which rescue analgesia administered was noted.

2.7. Statistical analysis

Data was initially entered into the microsoft excel sheet from the customized proforma for analysis. MiniTab Version 17.0 was used for calculating the P values. Comparison of means between the two groups was done using unpaired 't' test. Descriptive statistics was presented in the form of numbers and percentages. A p value of <0.05 was taken as statistically significant. The final data was presented in the form of tables and graphs.

Sample size calculation based on difference of means of two independent samples

We used the following formula for sample size estimation:

$$n_i = 2\left(\frac{Z_{1-\alpha/2}+Z_{1-\beta}}{ES}\right)^2$$

where n_i is the sample size required in each group (i=1,2), α is the selected level of significance and $Z_{1-\alpha/2}$ is the value from the standard normal distribution

holding 1- α /2 below it, and 1- β is the selected power and $Z_{1-\beta}$ is the value from the standard normal distribution holding 1- β below it. ES is the effect size.

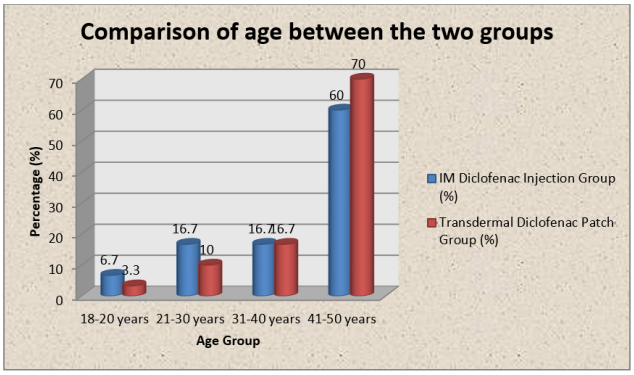

Fig. 1: Bar diagram showing comparison of age between the two groups

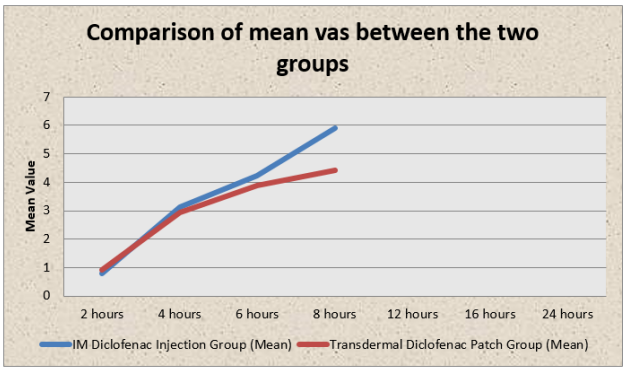

Fig. 2: Line diagram showing comparison of mean VAS between the two groups at different time intervals

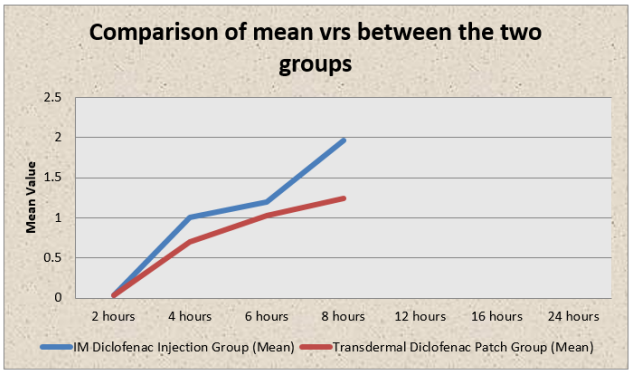

Fig. 3: Line diagram showing comparison of mean VAS between the two groups at different time intervals

The sample size obtained at 95% confidence interval with an 80% power of the study is 5 per group. Where a (type-I

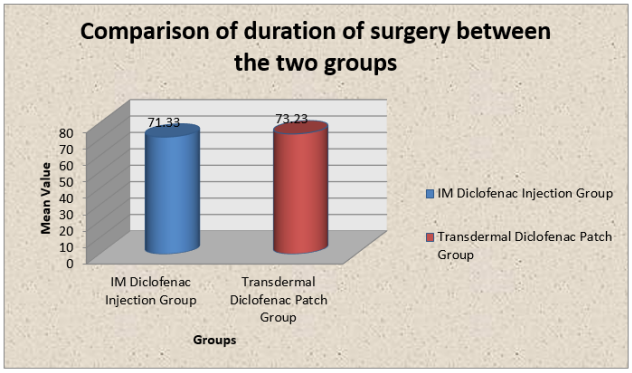

Fig. 4: Bar diagram showing comparison of duration of surgery between the two groups

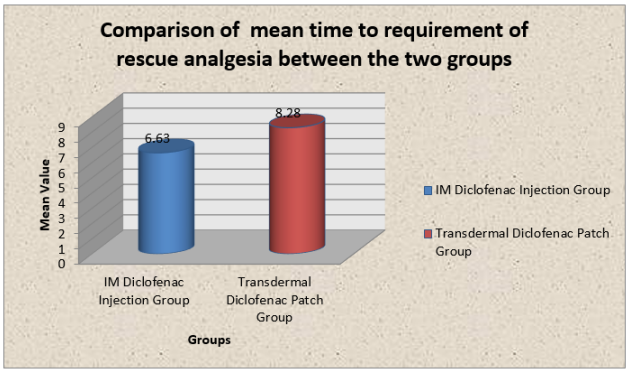

Fig. 5: Bar diagram showing comparison of mean time to requirement of first analgesia between the two groups

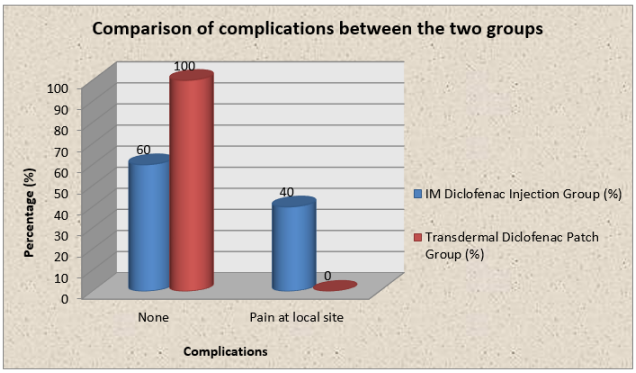

Fig. 6: Bar diagram showing comparison of complications between the two groups

error rate) = 0.05, b (power of the study) = 0.8. We used value of standard deviation of 1.566.

By putting these values in above mentioned formula we obtained a sample size of 5 in each group, but this sample size was too small and it would not have yield valid results. For statistical significance, we intended to include at least 30 patients per group.

Convenient sampling method was used in the present study.

3. Discussion

Analgesic intervention before surgical incision is a promising and innovative strategy for better pain control in the perioperative period. The goal of pre-emptive analgesia is inhibiting the nociceptive mechanism before they are triggered. It includes three objectives: (1) reduce pain and inhibition of inflammatory mechanism which is triggered by surgical incision. (2) Impedes pain memory response of the central nervous system. (3) Avoid the development of chronic pain by ensuring good control of postoperative pain.

Pre-emptive analgesia reduces postoperative pain as well as analgesia requirement. It has been associated with lesser side effects like nausea and vomiting contributing to a smooth and rapid recovery and reduced hospital stay.[12]

In our study the patients were comparable with respect to age, gender and demography wise distribution. In both the groups the mean duration of surgery was comparable and statistically not significant, with p value of 0.62.

The duration of analgesia was assessed by mean VAS score in both the groups and was statistically significant. In transdermal diclofenac patch group the mean VAS score at 2 hours were low that is,0.93 $\pm$ 1.01 which increased to 2.93 $\pm$ 1.02 at 4 hours, 3.87$\pm$0.73 at 6 hours and 4.41 $\pm$ 0.83 at 8 hours.

In IM diclofenac injection group similar trend was noted that is mean VAS score at 2 hours was 0.80 $\pm$ 0.99, which increased to 3.13 $\pm$ 1.01 at 4 hours, 4.23 $\pm$ 1.10 at 6 hours and 5.92 $\pm$ 0.41 at 8 hours.

The VAS score at 8 hours was more in diclofenac injection group than transdermal patch group, with p value of 0.00 and hence considered statistically significant.

The quality of analgesia was assessed by VRS score, where statistically significant difference was noted. In transdermal diclofenac patch group, the mean VRS score at 2 hours were low i.e. 0.03 $\pm$ 0.18 which increased to 0.70$\pm$ 0.47 at 4 hours, 1.03$\pm$0.18 at 6 hours and 1.24 $\pm$ 0.44 at 8 hours.

In IM diclofenac injection group similar trend was noted i.e. mean VRS score at 2 hours was 0.03 $\pm$ 0.18, which increased to 1.00 $\pm$ 0.00 at 4 hours, 1.20 $\pm$ 0.41 at 6 hour At 2 hours time VRS score was comparable in the transdermal diclofenac patch group with IM diclofenac injection group. P value was 1.000 which is statistically not significant. While at 4, 6 and 8 hours it is more in the IM diclofenac injection group than transdermal diclofenac patch group (p value was 0.001,0.045 and 0.000) which was statistically significant. (Figure 3)

VAS/VRS score after 12, 16 and 24 hours, the difference could not be calculated in both the groups because there was only 1 patient in the IM diclofenac injection group and the patient had already received rescue analgesia and the study ended at that point.

In the present study, mean time for the requirement of rescue analgesia in the transdermal diclofenac patch group is 8.28 $\pm$ 0.86 hours while in IM diclofenac injection group mean time of the first analgesia is 6.63 $\pm$ 0.81 hours and was statistically significant (p=0.000).

These findings correlate with Pragati et al[13] and Krishna et[14] al where transdermal patch group had duration of analgesia for 8 hours 6 minutes +_1 hour 4 minutes.

In IM diclofenac injection group 12 patients (40%) had pain at local site while in the transdermal diclofenac patch group, none of the patients had any of the side effects. These findings show that safety and compliance of the transdermal diclofenac patch is better.

Safety profile was documented in MASON et al[15] in which topical NSAIDs were used for chronic musculoskeletal pain and he found 6% local adverse event and only 3% systemic adverse event.

Safety profile was also documented in PREDEL et al[16] in which the diclofenac patch was used in blunt impact injuries and he found that the diclofenac transdermal patch was well tolerated.

3.1. Rationale of study

This study was conducted to assess the viability and efficacy of transdermal patches as pre-emptive analgesic to decrease postoperative pain and hence to decrease the hospital burden in terms of stay and cost.

4. Conclusion

It can be concluded that transdermal diclofenac patch (100 mg) is a better analgesic route than intramuscular inj. diclofenac sodium (75 mg) for pre-emptive analgesia in patients undergoing inguinal hernioplasty.

5. Limitation of study

We did not consider the s tress response in either groups, for which the measurement of serum cortisol would have been required. Also we did not include a placebo group as it would have been unethical.

6. Conflict of interest

None.

7. Source of funding

None

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