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Original Research Article

Efficacy and Safety of Transdermal Diclofenac Patch in Appendectomy Patients: Comparison with Intramuscular Diclofenac

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ABSTRACT

Background: The aim of this study was to compare the efficacy and safety of diclofenac transdermal patch with intramuscular diclofenac injections in appendectomy patients
Methods: Sixty participants of either sex scheduled for appendectomy were equally randomized into two groups. A transdermal diclofenac patch 100 mg was applied to the participants in the study group 3 hours prior to surgery. In the control group, 2 doses of 75 mg diclofenac sodium injections were given intramuscularly, first dose 2 hours after the surgery and second dose after 12 hours. In postoperative ward, assessment of intensity of pain was done by visual analogue scale (VAS) and verbal rating scale (VRS) for every six hours for a total duration of 24 hours. If a patient represented with VAS score >5 and VRS >2, necessitating urgent analgesia then in such situation there was a provision for rescue treatment, injection tramadol hydrochloride (50mg slow i.v. injection). Data were analysed using unpaired students t' test.
Results: Diclofenac patch provided effective analgesia for post appendectomy patients. Analgesia obtained with diclofenac patch was comparable with diclofenac injection and do not show any significant differences between the two. Also, no major adverse effect occurred due to application of diclofenac patch.
Conclusion: Diclofenac patch can be considered as an alternative option for pain management of post appendectomy patients, as it also improves compliance due to once daily application. The dose of diclofenac diethylamine patch may be increased to 200 mg instead of 100 mg to control post-operative pain more effectively in patient of appendectomy

Keywords: Transdermal, Diclofenac patch, Postoperative analgesia

INTRODUCTION

The International Association for the Study of Pain (IASP) has defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage". [1] Pain is an unpleasant localized sensation caused by the stimulation of sensory nerve endings called nociceptors, which are stimulated by the release of prostaglandins and other chemical mediators released from cells damaged by injury or inflammation. Surgery usually involves damage to tissues. Although ample evidence indicates that an efficacious postoperative pain treatment reduces patient morbidity and patient outcome, recent study demonstrated that about 50-70% of patients experience moderate to severe pain after surgery indicating that post operative pain remains poorly treated. [2] The pain of surgery is nociceptive (i.e. it is caused by tissue damage and is transmitted by normal physiological pathways), is acute and of short duration and subsides when the

damaged tissue heals. [3] Adverse effects of untreated postoperative pain include psychological effects (suffering, anxiety, depression, anger), stress response (sympathetic activation, hypertension, tachycardia, increased risk of myocardial infarction, stroke, renal failure), metabolic abnormalities, immobility (chest infection, venous thrombosis, pressure sore, delayed recovery) and development of chronic pain. The primary reason for trying to control pain after surgery is to relieve the suffering of patients, since it is the basic duty of all health care professionals to relieve pain and the most important indication for the treatment of pain after surgery is humanitarian. Effective pain control can attenuate the stress response to surgery, improves respiratory function and promotes better mobility. Reduction in postoperative complications and better mobility permit earlier discharge from hospital. Early and aggressive treatment of acute pain may prevent the development of chronic postoperative pain. For severe pain, the most effective treatment is a strong opioid such as morphine. A combination of different drugs improves the effectiveness of analgesia and by using smaller doses of each drug adverse effects are reduced. Control of postoperative pain optimally achieves the goal of providing adequate analgesia for the patient while avoiding any of the potential hazards of over sedation that may occur with excessive administration of opioid analgesics. [4] Postoperative pain medication may be considered as opioid and nonopioids classes of drugs. The opioid analgesics constitute by far the most important group of medications and are the mainstay of postoperative pain control. [5] But their efficacy is often limited by the development of tolerance, physical dependence, potential hazards of over sedation and respiratory depression. [4] Non-opioid analgesics potentially play an important role in postoperative pain control, particularly in the concept of the multimodal analgesic approach. Their ability to relieve pain and decrease opioid consumption is important.[6] Non-steroidal anti-inflammatory drugs (NSAIDs) are an important group of nonopioids analgesic medications particularly for the control of less severe pain and pain associated with a significant inflammatory component such as trauma. [5] The mechanism of NSAID action is to inhibit peripheral pain by blocking the enzyme cyclooxygenase, which converts arachidonic acid to prostaglandins. Prostaglandins are important mediators of inflammatory response and stimulate peripheral pain receptors. Long term use of NSAIDS causes adverse effects. However, short term NSAID ingestion in the postoperative period for analgesia is associated with a significant lower incidence of complications. Diclofenac is a well-established NSAID widely used in musculoskeletal disorders, arthritis, toothache, dysmenorrhea, for symptomatic relief of pain and inflammation. [7] Diclofenac is available in various forms like injectable, topical gel, ophthalmic solution, suppository and transdermal patch to treat pain. [8] Diclofenac inj. 75mg is used intramuscularly for adult and elderly for treatment of painful condition such as pain of kidney stones, osteoarthritis, rheumatoid arthritis, back pain, gout, injuries and fractures. [9] Acute appendicitis is one of the most common "Acute Surgical Abdomen" world over requiring surgical operation for total cure as well as to avoid complications. Appendectomy is practiced worldwide by conventional (open) method or by laparoscopic surgery. Studies show the presence of medium to intense pain in more than 80% patients. [10]

Diclofenac transdermal patch is a newly introduced delivery system for postoperative pain management. Oral bioavailability of diclofenac is about 50%. To avoid first pass metabolism, transdermal route is an alternative choice. In addition, transdermal patch offers added advantages such as painless technique, increased bioavailability, maintenance of constant and prolonged drug level, reduced frequency of dosing, minimization of inter and intra

patient variability, self administration and easy termination of medication, leading to better patient compliances. Diclofenac patch is a NSAID, it blocks certain substances in the body that are linked to inflammation. Diclofenac diethylamine is reportedly used for topical application. [11] Pradel et al used diclofenac patch for acute traumatic blunt soft tissue injuries and they found that patch was effective and well tolerated. [12] Bruhimann & Micheal reported efficacy of diclofenac patch in patients with knee osteoarthritis. [13] Alessandri et al found equal efficacy of diclofenac injection and patch for postoperative wound pain after laparoscopic gynecologic surgery. [14] Krishna and Nataraj reported that intraoperative 100mg diclofenac patch was as effective as intramuscular diclofenac injection 75mg for acute postoperative Pain (preemptive analgesic). [15]

Despite the fact that many analgesic drugs are available but still there is a search of an analgesic with minimum side effects and maximum analgesia with better patient compliance. Transdermal route is among the innovative drug delivery mechanisms which provides sustained drug delivery, needs once a day application and is convenient to use. There are very few studies regarding management of acute postoperative pain of appendectomy using diclofenac transdermal patch. Literature has been searched but very few studies have been done in this regard. Therefore, present study will be undertaken in patients undergoing surgery for appendectomy under regional (spinal) or general anaesthesia with the objective to evaluate and to compare the efficacy and safety of transdermal diclofenac patch with intramuscular diclofenac injection for postoperative analgesia.

MATERIALS AND METHODS

Study design

This was a prospective, open label comparative study. The present study was conducted in department of pharmacology and surgery at Pt. B.D. Sharma PGIMS Rohtak, approved by the Institutional review board.

Patient population

Sixty patients of either sex, 18-60 years of age scheduled for appendectomy and eligible as per inclusion and exclusion criteria were enrolled for this study. Enrolled patients were divided into two equal groups (30 each) and allocated to receive one of the 2 different treatments in an open fashion and were subjected to clinical assessment.

Inclusion criteria

Patients of either sex 18 to 60 years of age scheduled for appendectomy.

Exclusion criteria

1. Patients with history of asthma, urticaria, and hypersensitivity to any component of diclofenac patch or injection were excluded from the study.
2. Patients with severe hepatic and renal diseases and other co-morbid conditions (like diabetes, tuberculosis, & HIV)
3. Gastrointestinal tract related problems (gastritis, ulcers, bleeding & perforation)
4. Skin diseases (eczema, fungal infection, inflammation, burn wound)
5. Patient with history of alcohol abuse, blood (porphyria, bleeding or clotting disorders) and vascular disorder

Drug interventions

After taking detailed history from the patient general physical examination and systemic examinations were done. Patients were explained about the procedure, purpose, risks and complication of this study and how to interpret visual analogue scale (VAS) and verbal rating scale (VRS) postoperatively. A patient's information sheet was provided to every eligible candidate for the study and thereafter an informed written consent was taken from the participants of this study. Sixty enrolled cases for the study were divided randomly (using computer generated random numbers) into two groups of 30 each.

Group 1 patients received first dose of 75mg diclofenac sodium (3ml) intramuscular injection 2 hours after the

surgery and second dose was repeated 12 hours after the 1st dose.

Group 2 patients received transdermal diclofenac diethylamine patch 100 mg, 3 hours before the surgery and the patch was placed on the upper arm near deltoid region. Transdermal diclofenac patch was applied for a period of 24 hours.

On the previous day of the surgery patients were subjected to pre-anaesthetic check-up, investigation reports were checked accordingly. Vitals were monitored preoperatively and postoperatively. In postoperative ward, assessment for intensity of pain was done by visual analogue scale (VAS) and verbal rating scale (VRS) for every six hours for a total duration of 24 hours. If a patient represented with VAS score >5 and VRS >2, necessitating urgent analgesia then in such situation there was a provision for rescue treatment, injection tramadol hydrochloride (50mg slow i.v. injection)

Clinical assessments

Clinical assessments were done before and after operation (after drug administration).

End points for postoperative analgesia

Primary end points

Measurement for the intensity of pain postoperatively at 6, 12, 18 & 24 hours by

1. Visual analogue scale (VAS) [16] of 0 -10 points.
2. Verbal rating scale (VRS) [17] of scores 0-4.

Secondary end point

Number of times, requirement of rescue analgesic.

Safety assessment

Patients were assessed for the presence of any kind of side effects. If in case major toxicity to diclofenac injection or patch occurs in patients, necessitating discontinuation of treatment then the subjects are meant to be withdrawn from the study by giving appropriate treatment.

Statistical analysis

Results were analysed statistically using student's 't' test (unpaired). P value of less than 0.05 was to be considered as significant.

RESULTS

The demographic data of the present study showed ratio between male and female post-operative patient in group 1 as 30:5 and group 2 as 30:7 respectively. The mean age group for diclofenac intramuscular injection group and diclofenac patch group was26.4 and 31.8 respectively.

Visual analogue scale pain score : VAS pain score in patients of group 1 (diclofenac intramuscular injection) was mean 2.00±0.74, 2.20±0.71, 2.30±0.79 and 2.43 ±0.62 after 6,12,18 and 24 hours respectively during post-operative period. On the other hand VAS pain score in patient of group 2 (diclofenac patch) was mean 2.30±0.59, 2.40±0.67, 2.70±0.83 and 2.80±0.88 after 6, 12, 18 and 24 hours respectively during the postoperative period. A gradual increase in pain score was observed during post-operative period i.e. the pain score was minimal after 6 hours of surgery as compared to after 24 hours of surgery. VAS pain score was more in patients of group 2 (diclofenac patch) as compared to post-operative patients of group 1 (diclofenac intramuscular injection). These results indicated that mean pain score in patients received intramuscular diclofenac injection was less as compared to patients applied diclofenac diethylamine patch. Though the difference between the pain score in both the group was not statistically significant. However, most of the patients of group 2 (applied diclofenac patch) complained mild pain particularly at the 24 hours observation period. But no such complain was reported from the patients received diclofenac intramuscular injection.

Verbal rating scale score: VRS pain score in patients of group 1 (diclofenac intramuscular injection) was mean 1.13±0.34, 1.00±0.37, 0.90±0.30 and 1.33±0.47 after 6, 12, 18 and 24 hours respectively. On the other hand, VRS pain

score in patient of group 2 (diclofenac patch) was mean 1.30±0.46, 1.07±0.52, 1.07±0.45 and 1.60±0.67 at 6, 12, 18 and 24 hours respectively during post-operative period. A gradual increase in pain score was observed during post-operative period i.e. the pain score was minimal after 6 hours of surgery as compared to after 24 hours of surgery. VRS pain score was more in patients of group 2 (diclofenac patch) as compared to post-operative patients of group 1 (diclofenac intramuscular injection). These results indicated that mean pain score in patients who received intramuscular diclofenac injection was less as compared to patients who received diclofenac diethylamine patch. Though, the difference between the pain score in both the group was not statistically significant. However, most of the patients of group 2 (applied diclofenac patch) complained mild pain particularly at the 24 hours observation period. But no such complain was reported from the patients received diclofenac intramuscular injection. Secondary end point : In the present study very mild pain was observed in patients of both groups i.e patient who received intramuscular diclofenac injection 75 mg twice daily as well as patient who received diclofenac diethylamine 100 mg patch (single patch for 24 hours). The pain was well tolerated by most of the patients and rescue analgesia was not required by any patient. Pain score was comparatively more in patients with diclofenac patch as compared to the patient received intramuscular injection, particularly at 24 hours of observation period.

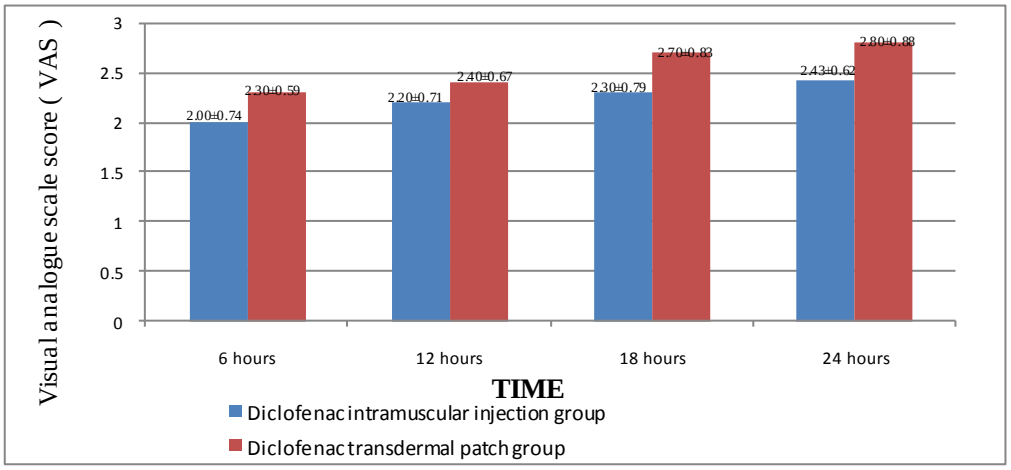

Figure 1: VAS showing pain score for diclofenac i.m injection versus transdermal patch in postoperative appendectomy patients

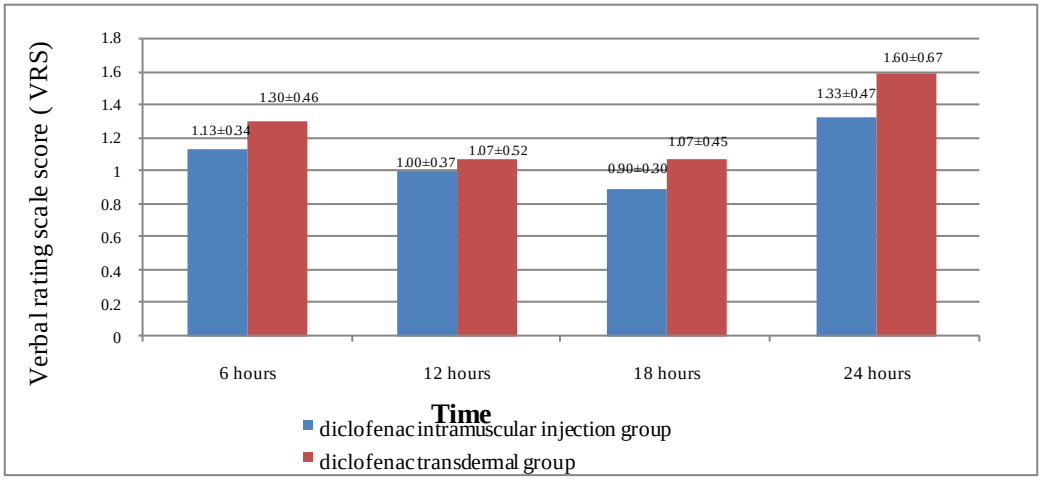

Figure 2: VRS showing pain score for diclofenac i.m injection versus transdermal patch in postoperative appendectomy patients

DISCUSSION

Results of the present study revealed that diclofenac sodium (75mg) intramuscular injection, twice daily produced significant analgesia in post-operative patients of appendectomy. Diclofenac diethylamine transdermal patch (100 mg, single patch for 24 hours) also produced analgesia in postoperative patients but efficacy of patch was somewhat less as compared to intramuscular diclofenac injection. Analgesic effect of diclofenac in post-operative pain may be due to reversal of peripheral sensitization by inhibiting prostaglandin synthesis via inhibition of cyclooxygenase 1 and cyclooxygenase 2 enzymes. Prostaglandins (PGE_2 and PGI_2) reduce threshold to stimulation of nociceptors causing peripheral sensitization. Prostaglandin E_2promotes via its receptors EP1 and EP4 the phosphorylation of transient receptor potential V1 (TRPV1) and other ion channels on nociceptors and increase their membrane excitability. Prostaglandins are potent mediators of pain that act directly at nociceptors and also increase nociceptors sensitivity. Thus by blocking the prostaglandin synthesis at the site of incision, diclofenac sodium increase pain threshold and reduces peripheral sensitization. In addition to peripheral action nonsteroidal anti-inflammatory drugs (NSAIDs) also have important central action in the spinal cord and brain. Both cox-1 and cox-2 are expressed in spinal cord and release prostaglandins in response to peripheral pain stimuli. Centrally acting prostaglandin $E_2$and perhaps prostaglandin D_2, prostaglandin I_2 and prostaglandin $F_{2\alpha}$ contribute central sensitization i.e an increased excitability of spinal dorsal horn neurons that causes hyperalgesia and allodynia. Cox-2 expressed in both neurons and glia cells contribute to central sensitization in early phase of inflammation. A role of cox-1 in nociception has also been implicated. Central sensitization reflects the plasticity of nociceptive system that is invoked by injury. [18] Thus it is possible that diclofenac produced analgesic effect in post-operative pain via antagonizing both cox-1 and cox-2 enzymes at the level of spinal cord and brain via antagonizing effects of prostaglandins which are involved in mediation of central sensitization. Diclofenac sodium is reported to be more selective for cox-2 as compared to cox-1 enzyme and selectivity of diclofenac sodium for cox-2 resembles that of celecoxib. Therefore, by blocking the cox-1 and cox-2 enzymes, diclofenac sodium reduces the central sensitization which is also responsible for post-operative pain. In addition diclofenac has been shown to reduce superoxide generation at inflammatory site and reduce intracellular concentration of arachidonic acid in leukocytes perhaps by altering its release or uptake. [19]

Results of study showed inappropriate or insufficient analgesia after application of diclofenac transdermal patch particularly after 24 hours of surgery. Since most of the patients complained mild but tolerable pain at the time of last reading i.e 24 hours of observation period. This indicates insufficient analgesia after transdermal patch after 24 hours only, though pain was adequately controlled at the time of 6, 12, 18, hours after surgery. The inadequate analgesic effect of transdermal patch may be explained on the basis of reduced concentration of diclofenac at 24 hours as the patch was applied once in 24 hours and diclofenac plasma concentration may be lower as compared to intramuscular injection which was given at 12 hour interval. Transdermal patch produced a slow and sustained concentration in the plasma for 24 hours. There is possibility that after 24 hours of application of transdermal patch diclofenac concentration was inadequate to control postoperative pain. Observation of this study suggests that in order to get appropriate post-operative analgesia with transdermal patch, either the frequency of application of patch should be increased i.e patch should be applied every 12 hourly or the dose of drug in the patch should be increased to 200 mg instead of 100 mg. Our

results at least in part are in agreement with the previous studies those reported analgesic effect of transdermal diclofenac patch in another different type of surgical conditions. Bruhelmann and Michael in a randomized, double blind, controlled clinical trial found that topical diclofenac patch was more effective in patients with knee osteoarthritis. [13] Predel et al reported that diclofenac transdermal patch was effective and well tolerated in patients with acute traumatic blunt soft tissue injuries. [12] Krishna and Nataraj reported that intaoperative 100 mg diclofenac patch was as effective as intramuscular injection (75mg) for acute postoperative pain when diclofenac was used as pre-emptive analgesic. [15] Krabayirli et al reported that diclofenac transdermal patch provided pain relief for postoperative laparoscopic surgery as effectively as intramuscular diclofenac injection. In this study transdermal or intramuscular diclofenac were reapplied 12 hours later and all patients were administered tramadol i.v. before surgery and post-operative pain management was done with tramadol using a patient controlled analgesia device. [20] Agarwal et al demonstrated efficacy of diclofenac transdermal patch in controlling pain of venous cannula. [21] Therefore, our results are not completely in agreement with the previous data reported. The differences in the present results and previous studies may be explained on the basis of types of surgery, different doses and protocols, and use of rescue analgesia by other workers.

Recent studies demonstrate that about 50-70% of patients experience moderate to severe pain after surgery indicating that post-operative pain remain poorly treated. Important reasons for this may be distinct mechanisms of incisional nociception compared to other pain conditions. Another reason might be the lack of an in depth knowledge about the pathophysiology and neuropharmacology of post-operative pain. [22] The pathophysiology of post-operative pain is multifactorial and predominantly of inflammatory nature from skin incision and tissue damage. Inflammatory cytokines, interleukins and prostaglandins produced from the arachidonic acid pathway induce a neuroinflammatory effect which sensitizes peripheral Aδ and C fibers. Many factors affect post-operative pain such as ischemia from retraction of tissue, disrupted blood supply, low pH and high lactate levels at the site of incision, types of surgery, preoperative risk factors (anxiety, depression, sleep disturbances, genetic susceptibility), intraoperative amount of tissue damage, repeated surgery, chemotherapy and radiotherapy can contribute to persistent postoperative pain. Therefore recently multimodel regimens are recommended for most effective post-operative pain management. [23-26]

Results of the study demonstrated significant analgesic effect after transdermal dicolfenac patch in appendectomy patients. Since, during surgery there is tissue damage by incision and pain of appendicitis may also be due to inflammatory processes. It is possible that diclofenac produced analgesic effect by reducing the concentration of local inflammatory mediators such as prostaglandins, bradykinins etc. which are responsible for sensitization of peripheral nociceptors. In addition to peripheral actions, diclofenac have some important central actions, most probably via blocking the cox-2 enzymes, which may be involved in controlling post-operative pain.

Safety analyses revealed no apparent serious adverse effects of diclofenac diethylamine patch. The diclofenac patch showed two cases of nausea and epigastric discomfort and one case of skin irritation having redness and itching at the site of application

At present it is difficult to propose the exact molecular mechanism of action of diclofenac patch in controlling postoperative pain in appendectomy patients. But study suggests that peripheral as well as central mechanisms may be involved and further studies are required to evaluate mechanisms of action of diclofenac in post-operative pain.

Our study results revealed that when applied 3 hours before surgery a diclofenac 100 mg transdermal patch had effectively reduced pain in appendectomy patients. Based on our observations, with proper time schedule application of transdermal diclofenac patch in appendectomy patients can be considered as safe and effective method of pain management. Diclofenac intramuscular injection provides better pain relief compared to diclofenac transdermal patch.

Study suggests that 200 mg transdermal patch may be better option in postoperative appendectomy pain control

CONCLUSION

Diclofenac patch provided effective analgesia for post appendectomy patients. Also, no major adverse effect occurred due to application of diclofenac patch. Therefore it can be considered as an alternative option for pain management of post appendectomy patients, as it also improves compliance due to once daily application. The dose of diclofenac diethylamine patch may be increased to 200 mg instead of 100 mg to control post-operative pain more effectively in patient of appendectomy

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