



**A COMPARISON OF DICLOFENAC PATCH AND INTRAMUSCULAR DICLOFENAC FOR POSTOPERATIVE ANALGESIA IN ABDOMINAL HYSTERECTOMY UNDER SPINAL ANAESTHESIA-A PROSPECTIVE, RANDOMIZED CLINICAL STUDY**

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**ABSTRACT**

**Introduction:** Immediate postoperative period is very crucial and pain is maximum during first 24 hours. If patients are kept pain free during this period, it leads to vitally stable postoperative period which in turn leads to early recovery. The aim of this study was to compare the analgesic efficacy of diclofenac sodium via two different route, intramuscular (IM) and transdermal in the management of postoperative pain. **Method:** After informed written consent, 60 patients of ASA grade I-III, scheduled for abdominal hysterectomy under subarachnoid blockade were randomized into two groups. Group TP (n=30) received transdermal diclofenac patch 3 hours before surgery and group IM (n=30) received intramuscular diclofenac sodium 30 min before the end of surgery. Transdermal or IM diclofenac were repeated 12 hours later. Postoperative visual analogue scores (VAS), haemodynamic data, requirement of rescue analgesic, patient satisfaction and adverse reaction if any were recorded every 2 hourly over 24 hours period. If VAS values were >4, 2mg/kg tramadol was given intravenously as rescue analgesia. **Result:** Postoperative VAS, haemodynamic data, requirement of rescue analgesia and patients satisfaction were comparable in both the groups (p>0.05). IM diclofenac has more side effects. **Conclusion:** Diclofenac transdermal patch provided postoperative pain relief as effectively as IM diclofenac for abdominal hysterectomy, without any significant side effects.

**KEYWORDS:** Diclofenac, Transdermal, Intramuscular, Postoperative pain and analgesia.

**INTRODUCTION**

Abdominal hysterectomy is one of the most commonly performed surgeries. In 2003, over 600,000 hysterectomies were performed in the United States alone, of which over 90% were performed for benign conditions.<sup>[1]</sup> Pain following abdominal hysterectomy is inflammatory in nature occurring in response to tissue injury and is accompanied by a neurogenic inflammation. Injured tissues will release various substances, such as potassium, prostaglandins, histamine, bradykinins that are pronociceptive and will also evoke an immune response.<sup>[2]</sup> These inflammatory and immune factors will sensitize the nociceptive receptors directly within the lesion and in the surrounding neurons. Primary hyperalgesia, which follows the release of these factors, may be measured as a lowered pain threshold in and around the lesion. NSAID's ability to inhibit prostaglandin synthesis, results in its anti-inflammatory activity, as well as contribute to its efficacy in relieving pain associated with inflammation. Secondary hyperalgesia is a phenomenon that refers to sensitization that occurs within the central nervous system.<sup>[3]</sup> Opioids interact with specific transmembrane G-protein coupled

binding sites termed opiate or opioid receptors. These receptors are located primarily in the spinal dorsal horn and other regions of the central nervous system that process affective and suffering aspects of pain perception.<sup>[4]</sup>

Although ample evidences indicate that an efficacious postoperative pain treatment reduces patient morbidity and improves patient outcome, in accordance with recent studies about 50–70% of patients experience moderate to severe pain after surgery indicating that postoperative pain remains poorly treated.<sup>[5]</sup> Various agents used for this purpose including acetaminophen, NSAIDs, opioids, glucocorticoids etc. Among these, much literature available for use of opioids to allay anxiety & post-operative pain. Because of documented problems with opioids like incomplete amnesia, histamine release, prolonged postoperative respiratory depression, increased blood volume requirement secondary to vasodilatation & hypotension diminished the popularity of earlier opioids as a sole analgesic agent.<sup>[6]</sup> Now a days apart from the traditional opioid analgesics, use of parenteral and oral NSAIDS is becoming more popular

for post-operative pain relief and diclofenac is one of them.<sup>[7,8,9]</sup>

Diclofenac is an analgesic-antipyretic-anti-inflammatory drug. It inhibits prostaglandins synthesis by inhibiting cyclooxygenase enzyme. Parental route (intramuscular) of admission is most commonly employed for pain relief. But it had a lot of short coming and may produce discomfort on injection and undesirable side effects like nausea and vomiting. Other alternative routes includes intravenous, suppository and transdermal route. Transdermal route has advantage of being painless, nonirritant and increase bioavailability.<sup>[10]</sup>

Though transdermal route has distinct advantage over parental route, there are very less studies which compared transdermal and parental route in patient undergoing abdominal hysterectomy. So the present study was undertaken in patients undergoing elective abdominal hysterectomy, under subarachnoid block with an objective to evaluate the efficiency, patient's tolerability, adverse events of transdermal diclofenac patch with intramuscular diclofenac for postoperative analgesia.

## MATERIALS AND METHODS

**Study Design:** A Prospective, Open, Single centric, Randomized clinical study.

**Study Duration:** 2 Years.

After written informed consent from patient, this prospective, randomized, clinical trial was carried out in patients of 40 – 80 years of age, belonging to ASA physical status I, II, having BMI  $\leq 30$  kg/m<sup>2</sup> and scheduled for elective abdominal hysterectomy under spinal anaesthesia at Late Shri Lakhiram Agrawal Government Medical College, Raigarh, Chhattisgarh. Patients with peripheral neuropathy, allergy to local anaesthetics or drug used in study, history of acid peptic disease, coagulopathy, cardiovascular disease and refusing to participate were excluded from the study.

### Preoperative preparation

The enrolled patients were randomly allocated by computer generated random number sequence in one of the two groups.

Group TP (n=30): Transdermal diclofenac patch of 100 mg was applied 3 hours before start of surgery.

Group IM (n=30): Diclofenac sodium 75 mg (3 ml) by intramuscular route was given half an hour before end of surgery.

Transdermal or IM diclofenac were repeated 12 hours later.

The patients were kept nil by mouth since 10.00 pm night before the surgery. In pre anaesthetic preparation room monitoring for vital parameters like Heart Rate (ECG), Mean Arterial Pressure (NIBP), Peripheral

oxygen saturation(Pulse oxymeter) were established and intravenous line was secured with 18G cannula.

### Premedication

(1) Tablet Alprazolam 0.5mg on night before surgery.

(2) Midazolam 1mg intravenous 30 minutes prior to surgery.

For surgery, under strict aseptic and antiseptic precautions patients were given subarachnoid block in lateral position in L3-L4 intervertebral space using 25G spinal needle with 3.5 ml of 0.5% hyperbaric Bupivacaine.

Post operatively, pain was assessed using VAS for the next 24 hours every 2 hourly. The goal is to keep VAS  $\leq 4$ . If any time VAS is  $>4$ , tramadol 2mg/kg intravenous will be given as rescue analgesic.

Minimum standard monitoring was continued up to 24 hours. Visual analogue scale (VAS), use of rescue analgesia, patient satisfaction score (excellent =3, good =2, poor =1) and complication (nausea/vomiting, abdominal pain, hypotension, urinary retention, itching, dislodgement/loosen/peel off, local site reaction and injection pain) if any were noted postoperatively for the next 24 hours every 2 hourly.

### Visual analogue score

VAS score is a psychometric response scale which is subjective. When responding to VAS system respondent specify their level of agreement to a statement by indicating a position along a continuous line between to end position.

0 1 2 3 4 5 6 7 8 9 10  
 |-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|

0 --- No pain  
 1 to 4 --- Mild pain  
 4 to 7 --- Moderate pain  
 8 to 10 --- Severe pain

### Statistical analysis

Considering post-operative analgesia as the main outcome measure of interest in this study with at least 10% efficacy shown by the study group, minimum 20 patients was required per group with the permitted alpha error of 0.05 and beta error of 0.2. With permitted beta error of 0.2, the power of study stands out to be 80%. To overcome with data loss, study dropouts and exclusion criteria, we enrolled total of 60 patients. Data collected was analysed as mean  $\pm$  SD and % which ever applied. Statistical analysis was done by graph pad instat 3.0 software. Inter group comparison between two groups was done using the unpaired student T test for quantitative data and chi square test for qualitative data ( $p < 0.05$  was considered as statistical significant).

## RESULTS

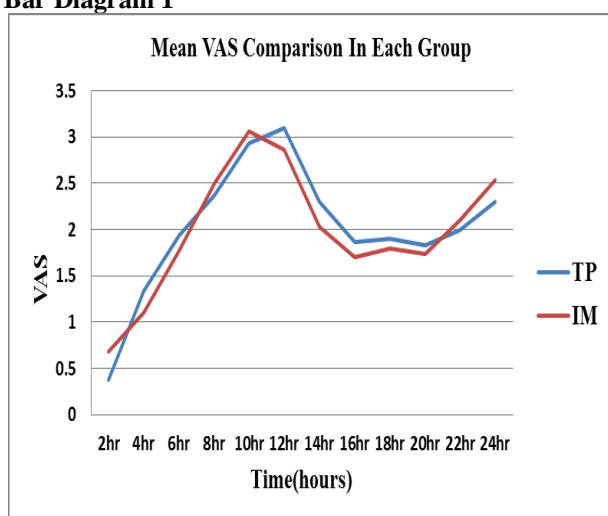
Table 1: Patient Characteristic.

PATIENT CHARACTERISTICS	GROUP TP (n=30) (Mean ± SD)	GROUP IM (n=30) (Mean ± SD)	P VALUE
Age (Years)	41.55 ± 5.21	42.03 ± 5.85	>0.05
Weight (Kg)	53.10 ± 7.54	54.50 ± 10.25	>0.05
Height (cm)	156.00 ± 2.69	155.40 ± 3.46	>0.05
ASA Physical Status (I/II)	9/21	7/23	>0.05
Duration of Surgery (min)	73.00 ± 17.78	72.66 ± 16.50	>0.05

As shown in **table 1**, patient characteristics in terms of age, weight, height and ASA physical status were comparable among the two groups of patients. Duration of surgery was also comparable in the two groups. ( $p > 0.05$ ).

**Vas Pain Score**

Comparison of Visual Analogue Score at 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24 hours was comparable in each group and difference was not significant statistically ( $p > 0.05$ ).

**Bar Diagram 1****Rescue Analgesics**

In group TP, majority of the patients required rescue analgesics between 9 - 16 hours. In group IM, majority of the patients required rescue analgesics between 0 - 8 hours.

**Doses Of Rescue Analgesics Required In 24 Hours**

On comparison of doses of rescue analgesia required, 5 patients in each group required one injection of rescue analgesia while 1 patient in each group required two injections in 24 hours. Hence there was statistically no significant difference in total dose of rescue analgesics required in group TP as compared to group IM.

**Patient Satisfaction Score**

Patient's mean satisfaction score at POD 1 (post-operative day) was comparable in each group and not significant statistically ( $p > 0.05$ ).

**Vitals**

Comparison of Patients Heart Rate, pulse, oxygen saturation and respiratory rate at 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24 hours was comparable in each group and difference was not significant statistically ( $p > 0.05$ ).

**Complications**

The diclofenac patch was well tolerated with 1 minor case of erythema and redness. In diclofenac intramuscular injection treated group 3 cases (10%) shows signs of erythema, induration & oedema associated with moderate pain, another 3 cases (10%) of gastric upset (abdominal pain and heart burn) have been reported.

**DISCUSSION**

Postoperative pain remains an important area of research for introduction of new modalities of treatment with enhanced effectiveness at the same time with lesser side effects. The advantages of effective postoperative pain management include patient comfort and therefore satisfaction, earlier mobilization, a reduced risk of deep vein thrombosis, fewer pulmonary and cardiac complications, faster recovery, reduced patient morbidity, reduced cost of care and improve the overall patient's outcome. Despite the obviously simple nature of surgical incision, however, perioperative and specifically postoperative pain remain under evaluated and poorly treated. Recent surveys suggest that 80% of patients experience pain after surgery, 11% having severe pain, and that pain delays recovery in 24% of patients undergoing ambulatory surgery. The possible reason could be distinct mechanism of incisional nociception, compared to other painful conditions. Another reason might be lack of knowledge in depth regarding the pathophysiology and neuropharmacology of postoperative pain.

Postoperative pain should be cured to alleviate nociception induced responses, such as the endocrine, metabolic and inflammatory responses to surgery which activates autonomic reflexes with adverse effects on organ function and reflexes leading to muscle spasm.<sup>[11]</sup> The autonomic over activity results in increase in heart rate, peripheral vascular resistance, arterial blood pressure and myocardial contractility which culminate in increased oxygen consumption from increased cardiac work. The combination of increased myocardial oxygen demand and decrease oxygen supply can be detrimental

in patients with coronary artery disease and may lead to myocardial ischemia and infarction.<sup>[12]</sup> Untreated or poorly treated postoperative pain increases incidence of nausea and vomiting. Increased sympathetic activity can lead to increased urinary sphincter tone and subsequent urinary retention.<sup>[12,13]</sup> The somatic pathway stimulation activates hypothalamic-pituitary axis which is followed by secretions of pituitary hormones. The limitation of movement caused by pain lead to marked impairment in muscle metabolism resulting in muscle atrophy, fatigue and delayed return to normal muscle function.<sup>[12,13]</sup> Psychological consequences due to inadequate pain relief include anxiety, fear, anger, depression and reduced patient satisfaction as well. So, it is a prime duty of an anaesthesiologist to provide postoperative analgesia to make patient more comfortable and relax after surgery.

Total abdominal hysterectomy is considered to be a major surgery with moderate to severe postoperative pain levels, with a small percentage of women suffering from chronic pain latter on, possibly as a result of inadequately treated acute pain after surgery.<sup>[14,15,16,17]</sup> Also this surgery can be done both under regional and general anaesthesia depending on how extensive the surgery is and the preference of the patient and surgeon.

Although opioids are effective postoperative analgesics, but their efficacy is often limited by the development of tolerance, physical dependence, potential hazards of over sedation and respiratory depression.<sup>[18]</sup> Among the non-opioid group of drugs NSAIDs have gained increasing popularity in treating postoperative pain specially diclofenac. The actions of diclofenac appear to be associated principally with the inhibition of prostaglandin synthesis - by inhibiting cyclooxygenase - the enzyme that catalyzes the formation of prostaglandin precursors (endoperoxides) from arachidonic acid. Alone or in combination with opioids they decrease postoperative pain. Topical application of NSAIDs has been reported to be effective in decreasing both acute and chronic pain.<sup>[19]</sup> Parenteral or oral administration of diclofenac has its own adverse effects and it also carries boxed warnings. Transdermal patch which is a new innovation in the drug delivery system offers many advantages such as painless administration of drug, increased bioavailability, maintenance of constant and prolonged drug level, reduced frequency of dosing, minimization of inter and intra patient variability, easy self-administration and easy termination of medication, leading to better patient compliance.<sup>[20]</sup> It also offers a good option for those patients who are unable to administer drug orally. In addition, topical NSAID's have been associated with a lower incidence of gastrointestinal adverse effects compared with systemic administration of this medication.<sup>[21]</sup> As it bypasses first pass metabolism in the liver, a transdermal drug administration also overcomes concerns regarding drugs that are poorly absorbed in the gastrointestinal tract. As safety is concerned, topical NSAIDs have potential advantage over parenteral NSAIDs.

In one study, the authors demonstrated that because of low systemic concentrations, topical NSAIDs have a reduced risk of upper gastrointestinal complications, such as gastric ulcers and other gastrointestinal symptoms like dyspepsia.<sup>[22]</sup> But an important concern with regard to transdermal drugs delivery is its prolonged duration of onset and offset compared to intravenous or intramuscular medication which can be used as when needed to control pain.<sup>[23]</sup> This disadvantage can be overcome by proper planning and careful timing schedule before application in order to get effective results. Therefore we have applied transdermal patch 3 hours before the start of surgery. In patients scheduled for surgery these agents are applied prior to the surgical intervention i.e. in anticipation to pain and not after the patient experiences pain, this is due to the long duration of its onset.

The present study shows that **analgesic efficacy** (using VAS score) was comparable in both the groups and result of this study was comparable with previous studies.<sup>[20,24,25,26,27,28,29]</sup>

One study showed that transdermal patch had better analgesic efficacy than diclofenac intramuscular injection,<sup>[30]</sup> while another study had superior result with intramuscular injection.<sup>[31]</sup>

**Patient's mean satisfaction score**, in the present study at postoperative day 1, was comparable in each group ( $p>0.05$ ).

Regarding **requirement of rescue analgesia**, 6 patients (20%) in each group required rescue analgesia though the timing of rescue analgesia was different. VAS score is subjective measurement of pain. So, individual variability in pain perception, lower threshold of pain in some patient may cause more requirement of rescue analgesia in such patients.

**Safety analyses** revealed no apparent serious adverse effects with transdermal patch. The safety profile of diclofenac patches has also been emphasized by Mason *et al*, in their systematic review on the use of topical NSAIDs in the UK and by studies reporting the use of the diclofenac transdermal patch in osteoarthritis as well as in in sports-related injuries.<sup>[32]</sup> Lower plasma concentration achieved with topical NSAIDs application is associated with reduction in systemic adverse effects.

Though we did not calculate the cost effectiveness between the two groups which can be the limitation of our study but it is obvious that intramuscular injection is cheaper than transdermal patch.

Our study results revealed that when applied 3 hours before surgery a diclofenac 100 mg transdermal patch had effectively reduced postoperative pain in patients of abdominal hysterectomy. And based on our observations, with proper time schedule application of transdermal

diclofenac patch in postoperative patients of abdominal hysterectomy can be considered as efficient as diclofenac intramuscular injection in terms of analgesia.

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