

Comparative Study of the Effects of Transdermal Patch versus Intra Muscular Diclofenac Sodium in Early Post-Operative Period after Hysterectomy under Spinal Anaesthesia

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Abstract: ***Background:** Pain management in immediate postoperative period is an extremely important. As oral medication is not possible at early post-operative period, injectable analgesia most commonly used at this time. It is painful and full of side effects. As the understanding of pain pathophysiology and treatment is increasing now a days, new routes of drug delivery are being discovered with the objective of blocking pain at peripheral sites, with maximum action of drug and minimal systemic effects. **Methods:** In a similar effort we compared the analgesic effects of diclofenac transdermal patch (100mg) and diclofenac intramuscular injection (75 mg). 160 eligible cases were selected for study on first come first basis and randomization was done in 2 groups using "Sealed envelope" method in the management of post-operative pain in terms of adverse effects, efficacy, duration, quality of analgesia on visual analogue scale of both. **Results:** It was concluded that transdermal patch of diclofenac had advantage over intramuscular diclofenac in being almost free of deleterious local side effects like skin erythema, pruritus, oedema, abscess, necrosis and this was significant. But at the same time diclofenac patch was as effective as diclofenac injection in providing post-operative analgesia. **Conclusions:** Patch has many advantages over intramuscular and useful even if the patient is nauseous or vomiting but its use in routine practice is not so common.*

Keywords: Diclofenac transdermal patch, Intramuscular injection, Pre-emptive analgesia, post-operative analgesia.

1. Introduction

Pain as defined by the International Association for the Study of Pain (IASP) is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage"¹.

It is a major symptom in many medical conditions and can interfere with a person's quality of life and general functioning².

Pain is frequently the result of nociception, an activity in the nervous system that results from the stimulation of nociceptors. This activity is carried to the brain, usually via the spinal cord, conveys information, about damage or near damage in body tissues. Pain is the conscious experience of sensorial information and a feeling of unpleasantness that manifests as a result of nociception.

Pre-emptive analgesia is defined as a treatment that is initiated before surgery in order to prevent the establishment of central sensitization evoked by incision and inflammatory injuries occurring during surgery and in the early post-operative period³. Owing to this 'protective' effect on the nociceptive system, pre-emptive analgesia is more effective than a similar analgesic treatment initiated after surgery. As a result, pre-emptive analgesia can reduce immediate post-operative pain and also prevent the development of chronic pain by altering the central sensory processing resulting from incisional injury (i.e. intra-operative period) and inflammatory injuries (intra-operative and post-operative period). The timing of analgesic administration is crucial and depends on pharmacokinetics of the analgesic agent used, so

that the peak analgesic effect occurs just before emergence from anaesthesia^{4,5}.

Diclofenac sodium belongs to the non-steroidal anti inflammatory drugs (NSAIDs) class of drugs. It helps to reduce inflammation and pain by blocking the production of COX and PG's that mediate inflammation, pain, stiffness, tenderness, swelling and increased temperature.

2. Transdermal Patch

The use of adhesive skin patches (Transdermal Drug Delivery Systems-TDDS) to deliver drugs systemically for post-operative analgesia is a relatively new phenomenon. They are shown to provide a steady plasma concentration of the drug, improved patient acceptability because of no discomfort of administration and once a day to once in three day application. All these factors increase the patient compliance to the therapy⁶.

In the recent past transdermal patches have been developed as an innovative topical delivery system for diclofenac that offers the advantage of sustained drug delivery. They are defined as a medicated adhesive patch which is applied on the skin to release a specific dose of medicine with a predetermined rate of release through the skin to reach into the bloodstream. These patches decrease the incidence of systemic adverse effects in comparison to oral drugs, due to lower plasma concentrations⁷.

Predel et al.⁸ used diclofenac patch for acute traumatic blunt soft tissue injuries and they found that the diclofenac patch was effective, well tolerated and reported no significant

adverse events with diclofenac when compared to placebo.

The aim of the our study is to compare the effect of 100 mg transdermal patch of diclofenac sodium and 75 mg intramuscular diclofenac sodium in terms of:

- Proportion of cases experiencing side effects till rescue analgesia given.
- Post-operative analgesia duration (Time between study drug administration to rescue analgesia administration at VAS score 3).

3. Materials and Methods

The study was be conducted in the Department of Anaesthesiology, Sawai Man Singh Medical College and Attached Group of Hospitals (MAHILA HOSPITAL), Jaipur. It was Hospital based Prospective Randomized Interventional comparative study.

The sample size required was 80 in each group at 95% confidence level and with 80% power.

- **GROUP A-** Intrathecal hyperbaric Bupivacaine (0.5%) 3ml (15mg) plus Intramuscular Diclofenac sodium (75mg) given just after spinal anaesthesia.
- **GROUP B-** Intrathecal hyperbaric Bupivacaine (0.5%) 3ml (15mg) plus Transdermal patch of Diclofenac sodium (100mg) applied just after spinal anaesthesia.

Inclusion criteria

- ASA grade I, II.
- Female between 35-55 years.
- Weighing between 45-75 kg.
- Height >145 cm.
- Scheduled to undergo elective hysterectomy.
- Duration of surgery about 60-90 minutes.

Exclusion criteria

- Any contraindication of spinal anaesthesia.
- History of gastritis, asthma, urticaria, allergic type reaction due to NSAIDs, hypersensitivity.
- Stomach/ duodenal ulcer or bleeding.
- Inflammatory bowel disease, crohn's disease, ulcerative colitis.
- ASA grade III or above.
- Patient had CABG surgery in past.
- Severe liver or renal insufficiency.
- Patients not willing to participate in the study.
- Patients with neuropathies or nerve injuries.

Assessment

The selected patients were examined, thoroughly investigated and explained about the interpretation of visual linear analogue scale to determine the level of pain during the post-operative period. A visual analogue scale (VAS) involves use of 10cm line divided into 10 equal parts, wherein one end of the line represents worst pain imaginable and the other end represents no pain at all. VAS score would be serially assessed at half an hour interval starting from 60mins till the patient complains of pain (VAS at 3).

Duration of effective analgesia would be measured as time from the intrathecal drug administration to the patient's VAS score at 3 either in the recovery room or the ward, and would

be recorded in minutes. Patient's VAS 3 and administration of rescue analgesia constituted the end point of the study. Tramadol (100mg) would be given as rescue analgesic if required.

The quality of analgesia was recorded 30 minutes, 1hr, 2hr, 4hr, 6hr, 8hr, 10hr, 12hr. The patch was removed after 12 hours.

In addition to recordings of Pain score; vital parameters (hear rate, oxygen saturation, noninvasive blood pressure) and two segment regression were monitored. Besides this, the timing of the rescue analgesia (VAS score \geq 3) met with intravascular injection of tramadol (100mg) required was also noted.

Side effects like Gastritis, Nausea, Vomiting, Pain on injection site, Swelling on injection site, Pruritus/Skin irritation and any other were noted.

4. Observation and Results

The age, body weight, height and ASA status difference was not significant in the 2 groups.

Duration of surgery was also comparable in the two groups with no significant difference.

In our study, we observed that onset and duration of sensory and motor block was comparable in Group A and Group B which was statistically not significant.

The Observations are presented as side effects and Mean \pm SD or as Percentages as is applicable.

Table 1: Comparison of Side Effects

Side Effects	Group A (No. of patients)	Group B (No. of patients)
Gastritis	5	0
Vomiting	3	0
Pain on Site Injection	2	0
Swelling	1	0
Pruritus	1	0
Erythema	0	2

Table 1 shows Group B had advantage over Group A in being almost free of deleterious local side effects. 12 patients out of 80 of Group A had side effects and 2 patients out of 80 of Group B had side effects and this was significant.

Table 2: Duration of analgesia [Mean \pm SD] (95% confidence interval)

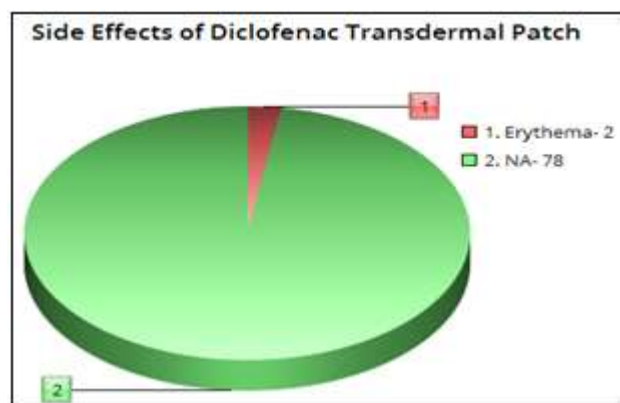
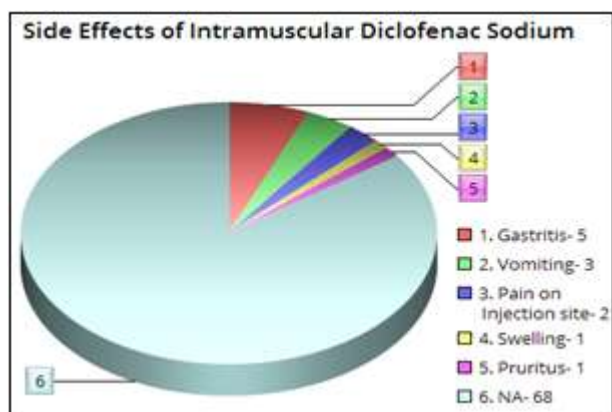
	Group A (n=80)		Group B (n=80)		P value
	Mean	SD	Mean	SD	
Duration of Analgesia (minutes)	419.56	20.36	413.62	19.73	0.0628
(Confidence interval)	(415.10-424.02)		(409.30-417.95)		

Table 2 shows the mean duration of analgesia and there was no significant difference ($p > 0.05$). So both diclofenac patch and diclofenac injection have same analgesic efficacy.

Table 3: Visual Analogue Score (Mean \pm SD)

	Group A (n=80) (Mean \pm SD)	Group B (n=80) (Mean \pm SD)	p-value
0 min	0	0	-
30 min	0	0	-
1 h	0	0	-
2h	0	0	-
4 h	0	0	-
6 h	0.47 \pm 0.65	0.55 \pm 0.81	0.49
8 h	0.06 \pm 0.37	0.04 \pm 0.33	0.72
10 h	0.30 \pm 0.46	0.27 \pm 0.45	0.68
12 h	0.54 \pm 0.50	0.61 \pm 0.49	0.37

Table 3 shows comparison of mean VAS between the groups which is statistically not significant at 6 and 8 hours ($p > 0.05$), not significant at 10 and 12 hours ($p > 0.05$).



5. Discussion

Transdermal delivery has a variety of advantages compared with the oral route. Particularly, it is used when there is a significant first-pass effect of the liver that can prematurely metabolize drugs. Transdermal delivery also has advantages over hypodermic injections which are painful, generate dangerous medical waste and pose the risk of disease transmission by needle re-use, especially in developing countries⁹.

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 circulation¹⁰. Its parenteral preparation is irritating and hence it is very painful at the site of administration. Development of skin, subcutaneous and

even muscle tissue necrosis (Nicolau syndrome), abscess formation etc. are rare but serious complications of intramuscular injections of NSAIDs¹¹.

So overall, transdermal drug delivery offers compelling opportunities to address the low bioavailability of many oral drugs, the pain and inconvenience of injections and the limited controlled release options of both. The various studies support our study in terms of efficacy and side effects of transdermal patch.

In our study, Group B had advantage over Group A in being almost free of deleterious local side effects. 12 patients out of 80 of Group A had side effects and 2 patients out of 80 of Group B had side effects and this was significant.

Similar result were made by **Selvi UPG et al.**¹² conducted a study and concluded that the transdermal diclofenac patch is a promising analgesic modality for the management of mild to moderate pain following surgery providing the evidence of its established analgesic potency with a lower incidence of systemic adverse effects.

Similar result were made by **Chaitanya NC et al.**¹³ and concluded that diclofenac transdermal patches have shown significant improvement in VAS score between the baseline and consecutive days and can be used in mild pain with lower adverse events.

In our study, we observed that duration of analgesia was comparable Group A and Group B which was statistically not significant between the groups ($p > 0.05$).

Karabayirli S et al.¹⁴ did a study and concluded that Diclofenac transdermal patch provided pain relief for post-operative laparoscopic surgery as effectively as intramuscular diclofenac.

Similar result were made by **Gulcin Ural S et al.**¹⁵ and concluded that in patients undergoing ambulatory laparoscopic cholecystectomy, a noninvasive application transdermal diclofenac sodium is as effective as intramuscular diclofenac sodium and can be preferred in post-operative pain treatment.

6. Conclusions

Patch has many advantages over intramuscular injection like self administration and self termination, having lesser local side effects (e.g., skin erythema, pruritus, oedema, abscess and necrosis), drugs enter the systemic circulation directly so drugs avoid first pass metabolism in the liver and drug destruction by stomach and digestive enzymes does not occur, useful when patients cannot swallow, even if the patient is nauseous or vomiting, useful even before and after surgery.

Precautions should be taken during apply patch like do not apply to hairy skin, skin that is broken, damaged, cut, infected, or covered by a rash, do not apply more or fewer patches, do not wear a patch while bathing or showering.

References

- [1] <https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698>.
- [2] Assessment of pain. *Br J Anaesth*. 2008;101(1):17–24. doi:10.1093/bja/aen103. PMID 18487245
- [3] Kissin I. Pre-emptive analgesia. *Anesthesiology* 2000; 93:1138-1143.
- [4] Amiya K. Mishra, MumtazAfzal, Siddhartha S. Mookerjee, Kasturi H. andyopadhyay, Abhijit Paul: Pre-emptive analgesia: Recent trends and evidences. *Indian J pain*.2013, 27(3): 114-12
- [5] Woolf CJ, Chong MS. Preemptive analgesia-treating post-operative pain by preventing the establishment of central sensitization. *AnesthAnalg* 1993;77:362-379
- [6] <http://www.ukessays.com/essays/nursing/prospective-randomized-double-blinded-placebo-nursing-essay.php>
- [7] Dhanapal S, Malli SN. Efficacy of Single Dose of Transdermal Patch as a Pre-Operative Analgesic in Root Canal Treatment – A Randomized Clinical Trial. *J Pharm Sci and Res*. 2016;8:125-127
- [8] Predel HG, Pabst H, Schäfer A, Voss D, Giordan N. Diclofenac patch for the treatment of acute pain caused by soft tissue injuries of limbs: a randomized, placebo-controlled clinical trial. *J Sports Med Phys Fitness*. 2016 Jan- Feb;56(1-2):92-9. Epub 2015 May 27.
- [9] Hawker GA, Mian S, Kendzerska T, French M. Measures of Adult Pain. *Arthritis Care & Research*. 2011;63(11):240–52.
- [10] Miller MA, Pisani E. The cost of unsafe injections. *Bull World Health Organ*.1999;77:808–811.
- [11] Lie C, Leung F, Chow SP. Nicolau syndrome following intramuscular diclofenac administration: a case report. *J OrthopSurg (Hong Kong)*. 2006;14(1):104-7.
- [12] Selvi UPG, Kamatchi D, Babu C, Keerthana S, Jeeva SVL. Comparison of Transdermal Diclofenac Patch with Intramuscular Diclofenac Injection as an Analgesic Modality Following Surgical Extraction of Impacted Mandibular Third Molars: A Cross Over Efficacy Trail. *Int J Sci Stud* 2016;4:117-123.
- [13] Chaitanya NC, Karunakar P, Garlapati K, Yeladandi M, Bidari P, Soni P. A comparative evaluation of diclofenac sodium transdermal patch, oral diclofenac sodium with intramuscular injections of diclofenac sodium in patients suffering from oral pain *Int J Pharm Investig*. 2017 Jul-Sep;7(3):132-136. doi: 10.4103/jphi.JPHI_52_17.
- [14] Karabayirli S, Demircioğlu RI, Muslu B, Usta B, Sert H, Gözdemir M. The comparative effects of transdermal and intramuscular diclofenac on postlaparoscopic surgery pain. *Surg Laparosc Endosc Percutan Tech*. 2012Aug;22(4):374-378.
- [15] Gulcin Ural S, Yener O, Sahin H, Simsek T, Aydinli B, Ozgok A. The comparison of analgesic effects of various administration methods of diclofenac sodium, transdermal, oral and intramuscular, in early post-operative period in laparoscopic cholecystectomy operations. *Pak J Med Sci*. 2014 Jan;30(1):96-100.