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Evaluation of Effectiveness of Diclofenac Transdermal Patch For Immediate Post Operative Analgesia in Post Lscs Patients in a Teritiary Care Centre

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Abstract: *Dicofenac patch is a novel approach to a less invasive advent of analgesia. Most of the older versions of analgesia were one or other way invasive, which needs the assistance of medical or para medical staff.In older methods like intramuscular or intravenous strict sterile precautions are necessary for proper outcome, sterility of the needle or person who is administering it is needed. Here this method eliminates the need for multiple injections, avoids first pass metabolism and is unaffected by first pass metabolism, definitive role in topical anaesthesia, acute pain management musculoskeletal and neuropathic pain.*
Diclofenac patches are available at strengths of 100mg, 200mg.
Materials and Methods*Sample size of 50 each selected for the study randomised by computer generated random number table method study group (I) administered 100 mgm transdermal patch of 100 mgm diclofenac and the control Group (II) patch is not administered.****Result and Conclusion****Quality of analgesia in the two groups compared by duration of post operative analgesia provided, VAS scoring and the mean dose of rescue analgesic needed. Standard deviation being 1 and 0.2 respectively for Group I and Group II patients. Group I patients mean duration of analgesia being 4.5 hrs and 0.7 hrs respectively. Mean VAS score and mean dose of the rescue analgesic shows from the study that transdermal patch is a comparably good analgesic than control patients. More than this study group peritoneum being a highly painful structure, being breached compared to musculoskeletal structures may be the reason for lesser duration of analgesia for the patch when compared to other clinical conditions.*
Keywords*:VAS - Visualanalogue scale, iontophoresis, electroporation, magnetophoresis, rescue analgesic, first pass effect, stratum corneum, posthoc analysis.*

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I. Introduction:

Even though management of pain is given more importance in palliative medicine, post operative patients need extensive analgesia consequent to tissue damage, intra-operative manipulation of tissues, and extensive retraction is needed for delivery of baby via LSCS. Pain is defined as unpleasant sensory and emotional experience associated with actual or potential tissue damage, as described by Hughes[1].

The use of skin as a route of drug deposition dates back to the era of Galen, The Father of Pharmacy, who developed the cold cream for applying over skin, the basic model behind the transdermal drug delivery system[2].

The skin is an easily accessible organ with a surface area[3] of 1.5 to $2m^2$. The non invasive nature is of administration and maintenance of steady plasma concentration of drug as long as patch remains results in desirable therapeutic effects for a prolonged period[4]. The transport of drugs across the epidermis to reach the site occurs by 3 pathways: 1. Intercellular; 2. Transcellular; 3. Transappendageal, which enables transfer of relatively large molecule and this pathway[5, 6] is of minor importance. The decline in drug levels following patch removal is dependent on context sensitive half life of drug depots in skin[5]. Patches can be single layered, multilayered, with reservoir system, matrix system or hybrid patches. Novel methods of drug delivery are iontophoresis, using USS waves used to transport invasive methods such as microneedles, electroporation, laser ablation, magnetophoresis, plus nano carrier and liposomes. Various physical methods, chemical enhancers, nano carriers, ultrasonic, electrical, magnetic and laser waves are used as a component of the patch or transdermal system to facilitate drug movement [2-4]. The third generation systems induce irreversible changes in the stratum corneum to hasten transport by use of microneedles, laser ablation, electroporation, jet injectors etc to the skin[6-8].

Post-operative pain management is headed by an operating team consisting of surgeons and anaesthesiologists. Intraoperative pain management has to be extended to the post operative period immediately to provide pre-emptive analgesisa. Diclofenac suppository has been extensively studied for its efficacy and safety as a postoperative analgesic. But transdermal patch, which is less invasive than suppository, can be administered by the patient himself. Narcotics and NSAIDS are the drugs easily available in the post operative period. Narcotic analgesia is associated with drowsiness, constipation, urinary retention, circulatory and respiratory disturbances in parturient. This in turn leads to decreased feeding of baby, decreased baby-mother bonding, hypoglycemia and seizures in baby consequent to an un-cooperative and sedated mother. Routine oral administration is impractical in post operative period. First pass metabolism, decreased patient compliance, painful and irritating parenteral administration of drugs; there comes the importance of transdermal patch. Development of skin, subcutaneous and injection site muscle tissue necrosis leading to abscess formation are rare but serious complication are rare this serious development is called "Nicolau" Syndrome following I/M Diclofenac injection.

Diclofenac sodium is a phenyl acetic acid derivative which is relatively nonselective cox inhibitor. It is one of the most potent NSAIDS in India. Diclofenac is supplied either as sodium or potassium salt. It bears the formula $C_{14}H_{11}C_{l2}NO_2$. Molecular mass is 296.148 g/mole[6], 99% protein bound, metabolised hepatically with no active metabolite. It is excreted mainly by biliary route and 1% excreted in urine. Diclofenac has analgesic, antipyretic and anti inflammatory properties. Diclofenac potency is substantially greater than that of indomethacin, naproxen and several other NSAIDS.

Oral diclofenac has substantial first pass effect, only 50% diclofenac available systemically.
Diclofenac transdermal patch is a new advanced novel drug delivery system that offers several advantages. Its bio-availability is 50%.

It addresses two significant problems posed by traditional oral dosage form, gastric irritation and need to consume 2-3 doses per day. The transdermal delivery route also scores over the gel as it is cream based, is nongreacy most importantly need not be applied at local site of pain. Transdermal patch with its unique profile addresses the problem covered by oral tablets.

It is a new advanced novel drug delivery system through the transdermal route, offers several advantages. Its bioavailability is 50%. It addresses the two significant problems posed by the traditional oral dosage form, local gastric irritation and the need to consume two to three doses in a day. The transdermal delivery route also scores over the gel as it is not cream based, is non greasy and most importantly it need not be applied at the local site of pain. The side effects of NSAIDS taken through the oral route especially their propensity to cause gastritis or ulcers often impede their long term use. Transdermal patch with its unique profile addresses these problems. Non steroidal anti inflammatory drugs such Ibuprofen, diclofenac and Nimusulide are commonly prescribed drugs for pain management conventionally. These drugs are administered orally or as injections. While NSAIDS are very effective, they are also known to cause local gastric irritation when consumed orally. This led to the search of an alternative drug delivery routes. Diclofenac transdermal patches are available in strengths of 100mg and 200mg.

The Patch is expected to exhibit excellent local action and to prevent the side effects such as the gastrointestinal lesion by applying to and inflammatory site so as to percutaneously absorb the effective component.

As a stratum corneum containing Keratin as a main component and contains a large amount of a fat soluble component such as fat, wax, and cholesterol. Therefore the skin has a physiological defensive function, a so called barrier function and as a result it is difficult to easily cause percutaneous absorption of the drug. Against drugs having a salt form, such as Diclofenac sodium the skin exhibits a strong barrier function.

On the other hand skin adhesive preparations are composed of rubber or acrylic high molecular weight material as a base material. These materials generally do not dissolve drugs sufficiently and it is quite difficult to uniformly dissolve the drug having the salt form such as Diclofenac sodium and maintain the dissolved state. It has been found that[8] IF Diclofenac sodium is contained in a pressure sensitive adhesive material layer in combination with an organic acid, Diclofenac sodium can be converted to free based Diclofenac in the pressure sensitive adhesive material layer. As a result the solubility of Diclofenac sodium is increased and transfer of the drug to the skin surface is facilitated, whereby Diclofenac sodium can easily penetrate through the stratum corneum as a barrier layer. BY concurrently using Diclofenac sodium and the organic acid, Diclofenac sodium is converted into free based Diclofenac having higher oleophilicity [9], the solubility of Diclofenac sodium in the pressure sensitive adhesive material is increased and Diclofenac can easily penetrate through the stratum corneum having the barrier function.

Systemic absorption after topical application depends primarily on the lipid solubility of drugs. However, only a few drugs penetrate intact skin. Absorption can be promoted by rubbing the drug incorporated in an oleogenous base or by use of occlusive dressing which increases hydration of the skin Transdermal patches are categorized in to three groups. Group I - This is the first generation patches consists of a drug reservoir enclosed on one side with impermeable backing and adhesive which contacts skin. Group II [Second generation]

patches where there is increased permeability to skin, reduced damage of deeper tissue and enhanced transport to skin Chemical enhancers, non cavitating ultrasound and iontophoresis protects inner tissues. Third generation patches [Group III] enhance far better skin penetration and preventing damage to deeper tissues. The transdermal patches of diclofenac sodium are available in strengths of 100 mg and 200 mg.

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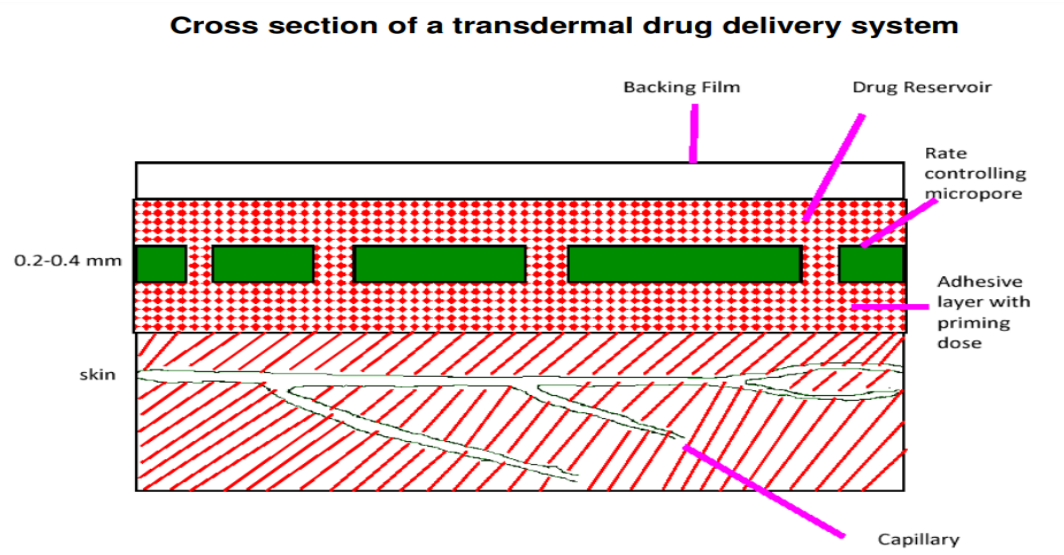


Common drugs for which transdermal patches used are timolol testosterone, verapamil, digoxin, insulin, prostagladin, ISDN, hyoscine, clonidine, nicotine and fentanyl ketotifen, piroxicam and lidocaine plasters used for herpetic neuralgia.

II. Materials And Methods:

This randomized clinical trial was conducted in the department of anesthesiology at, the women and children wing of Medical College, Trivandrum during the period 2006-2008. Institutional research committee and ethics committee approval were obtained before conducting the study. Informed consents were taken from all patients enrolled in to the study. We conducted this study in accordance with the principles laid down as per the declaration of Helsinki. In this study, we recruited 100 patients undergoing Lower Segment Caesarian Section under Lumbar subarachnoid (LSAB) block. A priori sample size calculation was done at the protocol stage.

Patients scheduled for elective or emergency LSCS under subarachnoid blockade were randomly recruited in to this study. We included only patients between 18 to 30 years. Only those having a height between 155 cm to 175 cm were recruited. ASA grade above III were excluded from the study. In addition, only those cases where the duration of surgery was not beyond 90 minutes with Initial Spinal Sensory level above T6 segment were included in this trial. Those cases with failed spinal anesthesia, inadequate spinal sensory level were excluded from the study. Moreover, those with previous hypersensitivity to NSAID, angioedema, urticaria and Bronchial Asthma, bleeding and coagulation disorders, severe renal disease, Congestive Cardiac failure, severe preeclampsia and hepatic insufficiency were excluded as well. In addition we did not include those patients having Acid peptic disease, Gastiritis, Malena and history of proctitis or Ulcerative Colitis in this study.

All patients were, in patients. Study was conducted in both emergency and elective caesarian section cases. Thorough preanaesthetic check up and investigations like Blood, Urine routine examinations, VDRL, HIV, HBsAg, Blood grouping and cross matching and bleeding time & clotting time are done prior to surgery. Inclusion and exclusion criteria were strictly followed. All elective cases pre-medicated with Ranitidine 150mg and metoclopramide 10 mg orally at 10 pm day before surgery and the same repeated at 6 am on the morning of surgery. In emergency caesarian section cases Inj. Ranitidine 50 mg 1/V and Inj. Metoclopramide 10 mg were given as premedication immediately before spinal anaesthesia. After premedication baseline blood pressure pulse rate and oxygen saturation were noted. Patients were randomized according to a computer generated random number table. Allocation was concealed. Study includes two groups of patients group I patch group. Group II - control group.

All patients were monitored with noninvasive blood pressure, pulse oximeter and continuous electrocardiography.

Pre-loaded with 250-500 ml normal saline. Patient positioned in the left lateral position, with hip and knee flexed, spine also flexed for administering spinal anaesthesia taking care of the monitors already attached. Patient's back prepared, wiped with iodine solution, followed by spirit, draped sterile under sterile precautions lumbar subarachnoid block at the level of L3-L4 or L4-5 using 23G Quincke needle, after freeflow of cerebrospinal fluid. 2ml of 0.5% heavy Bupivacaine administered. Patient immediately turned from the left lateral to supine position. Oxygen is administered via polymask and 15-30° left lateral tilt given.

Spinal Sensory level checked after few minutes and table tilt adjusted to keep sensory level at or above T4 – T6 segment level. Then the surgery started and once the baby delivered, Inj. Midazolam 1mg + I/V plus Inj. Oxytocin 20 units I/V infusion in 500ml normal saline administered via the I/V cannula in mother, were administered for the three study groups. Tilt of table was adjusted so that patient was in supine position. Rescue analgesic in the form of inj. Morphine 0.05mgm/kgwt plus or-0.01mgm/kgwt administered if any group of patient complained of pain after noting time, VAS score and dose of rescue analgesic needed to abolish pain. After closure of the surgical wound in layers up to this step procedure being same for 2 groups of patient's under study. At the end of surgery spinal sensory level again checked.

For the Group I - Patch Group patients, once surgery is over Diclofenac Sodium 100 mg transdermal patch is peeled off from the silver foil and the exposed patch is pasted 5 cm above the caesarian wound, time noted. Pulse rate and blood pressure are recorded.

In case of Group II patients no patch is placed. After surgery blood pressure and pulse rate and time were noted. inj. midazolam 1mgm i/v.

In the post operative period in the two groups under study, intensity of pain was assessed using VAS scoring system. visual analogue scale which is a 10 cm long horizontal line with no pain at one end and worst imaginable pain at other end. The distance from 'no pain' to the patient's mark numerically quantitates pain. visual analogue scale which is a 10 cm long horizontal line with no pain at one end and worst imaginable pain at other end. The distance from 'no pain' to the patient's mark numerically quantitates pain.VAS score of zero means no pain and score of 9 & 10 corresponds to severe degree of pain. VAS score of 5 & 6 indicates moderate degree of pain. VAS>5 cm in considered as moderate pain and it is a self assessment method for pain by patient himself when the numerical score is more than 5 patient has moderate pain and rescue analgesic in the form of inj. Morphine 0.05mgm/kgwt ± 0.01 mg/kgwt I/V incremental doses until patient is relieved of the pain in the two groups as suggested by VAS score. Total dose of rescue analgesic needed also recorded in the two groups. Time at which the rescue analgesic administered also noted, in the two groups.

Duration of analgesia extends from the time of placement of transdermal patch, to the time at which patient has moderate degree of pain occurs and rescue analgesic was administered. It was measured in hours.

All the patients in the two groups were observed for occurrence of nausea, shivering, vomiting, excessive bleeding, itching etc.

All data collected were entered in to a master chart and statistical analysis was done in R statistical software. Descriptive statistics are reported as mean and standard deviation for continuous data and median and interquartile range for non normal data. Categorical data were summarized as percentages and in absolute frequencies. Comparison of outcome between two groups were done with post hoc tests were conducted. A 'p' value less than 0.05 was taken as statistically significant.

III. Results:

A total of 100 patients were recruited in to this comparative study with 50 patients in each group. The median weight of the patient in the study was 61.0 [60.0; 63.0] kg and height 159 [158; 162] cm. There were 77 (51.3%) in the 18-24 age group and 73 (48.7%) patients in the 25-30 age groups. Baseline characteristics of the patients were comparable across the two groups (Table 1).

Table1: Baseline comparison across the groups.

	Control N=50	Patch N=50	p.overall
Weight	61.5 [59.5;63.0]	61.0 [59.2;61.0]	0.125
Height	159 [158;165]	159 [158;162]	0.825
Age:			0.602
18-24	28 (56.0%)	26 (52.0%)	
25-30	22 (44.0%)	24 (48.0%)	

There is a statistically significant difference between the duration of analgesia between the two groups (P value <0.001) (Table 2 and Figure1).

Table 2: Duration of effects across the two groups.

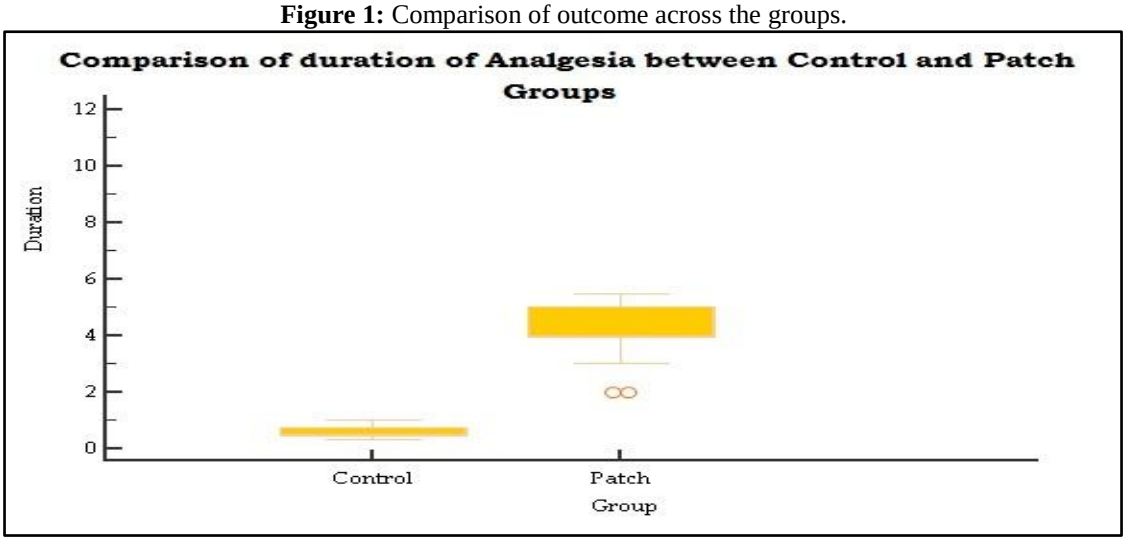
	Control N=50	Patch N=50	p.overall
Duration	0.75 [0.50;0.75]	5.00 [4.00;5.00]	<0.001

Post hoc analysis showed statistically significant different changes between patch and control.

Table 3: Post-hoc analysis

Factor	n	Average Rank	Different from factor nr	(P<0.05)
(1) CONTROL	50	25.50	(2)(3)	
(2) PATCH	50	75.50	(1)(3)	

Figure 1: Comparison of outcome across the groups.



IV. Discussion:

Duration of postoperative analgesia studied postoperatively using visual analogue scale (VAS). VAS is a method used to grade pain by self assessment by patients. Endpoint being appearance of moderate pain grade with VAS score>3 when rescue analgesic given in the form of injection morphine0.05mgm/kgwt ±0.01mgm/kgwt. incremental doses until the pain subsides. The dose of rescue analgesic needed is noted. Mean duration of analgesia provided by Group I patients Diclofenac patch is 4.5 hours with a standard deviation of 0.05. P value is 0.000 showing that it is significant at P value of 0.01 for control [Group II] patients immediately in the postoperative period injection. Midazolam 1mg i/v and the time at which moderate pain grade rescue analgesic given mean dose was higher compared to the patch group. Thereby showing that patch group has shown good quality of analgesia compared to the control group. Also the side effects in each group of patients is noted like nausea, vomiting, local irritation, allergy. Mean duration of analgesia produced by the control group is 0.7 hours with standard deviation 0.2 hours. 50 each patients were selected for Group II [control] and Group I [patch] group. Rescue analgesic given in the form of injection morphine 0.05mgm/kgwt ±0.01mgm/kgwt, as incremental IV dose until pain is relieved.

Diclofenac transdermal patches for postoperative shoulder pain was studied by Lennart Funk[10], Umaar Molajoa of Bridge Water Hospital, Manchester, United Kingdom. Major shoulder surgeries can now be performed as a daycare procedures thanks to advancement in minimally invasive technique and regional anaesthesia. Diclofenac patches have proven to reduce pain and inflammation in direct treatment of acute and chronic inflammatory conditions. They release the active ingredients over 12-24 hours period with less systemic side effect than oral forms and better patient compliance.

According to Galer BS[11], Rowbotham M, Perander J, Devers A, Friedman E topical diclofenac patch relieves minor sports injury pain. Alessandri[12], Lijoi found that topical diclofenac patch was effective for postoperative wound pain in laparoscopic gynaecologic surgery in randomised study. According to Bruhlmann

P[13] and Michael B.A in a randomised double blind controlled clinical trial that topical diclofenac patch was effective in patients with knee osteoarthritis. Diclofenac has been proved to have antibacterial action by virtue of inhibition of DNA synthesis[14]. The efficacy and tolerability of nonsteroidal anti inflammatory drug, DHEP plaster[15] in extra articular rheumatological disease.

Diclofenac has similar cox-2 selectivity to celecoxib, FDA medical officer David Graham concluded that diclofenac increases the risk of myocardial infarction. It is concluded that increased blood loss[16] increased duration of analgesia, and increased potency seen with diclofenac sodium.

In case of post LSCS patients for postoperative analgesia disadvantage of opioids is that it is secreted in breast milk produce sedation nausea vomiting respiratory depression, hypo ventilation and addiction liability. Significant amount reaching new born lead to decrease in the activity, improper feeding, decrease the alertness, inadequate burping by the mother.

NSAID drugs produce excellent preemptive analgesia as it is administered before waning of spinal anaesthesia. There is reduced incidence of opioids induced complications. The main advantages of patch over injectable diclofenac are:

1. Self administration and termination of metabolism by directly entering circulatory system without fist pass effect in metabolism
2. Lesser regional side effects unlike injectable diclofenac [erythema, swelling, pruritus].
3. Useful in dysphagia patients and perioperative periods and those with emesis, nausea, only disadvantage being longer onset of action

Statistical assistance availed from Dr Induprabha Yadav for this study.

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