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Comparative Study of Two Phamaceutical Forms of Nsaid for Pre- Emptive Analgesia in Post LSCS Patients

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Abstract
Background
Pre- emptive analgesia is one of the prerequisites for modest postoperative outcome. It provides optimal physiological effect after a stressful intraoperative period. Different pharmaceutical forms of the same analgesic differ in their onset of action at the target sites.
Materials and Methods
In this study, two pharmaceutical forms of the drug diclofenac are compared regarding their effectiveness. The sample size was 50 each for diclofenac100mg transdermal patch and diclofenac 100mg suppository in post LSCS patients where surgery was done under LSAB.
Result
In this study, it was proved that diclofenac suppository 100mg was more effective than diclofenac 100mg transdermal patch in providing post operative analgesia.
Conclusion
From this study, it was concluded that diclofenac 100mg suppository provided an efficient pre emptive analgesia in post LSCS patients. NSAIDS do not suppress respiratory reflexes in newborns and neonates compared to the opioids.
Keywords:
VAS – Visual Analogue Scale
SUPP – Suppository
TAB – Transverse Abdominis Blockade
LSCS – Lower Segment Caesarian Section
AVC – Area Under Curve
NSAID- Non Steroidal Anti Inflammatory Drugs

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I. Introduction

[1]Pain is one of the most unacceptable symptom accompanying caesarean section patients. Sufficient post-operative pain relief after caesarean is vital as it affects the adequate surgical recovery requirement of the parturient

Various advanced modalities of post-operative analgesia management in post lower segment caesarean section patients are available.The methods already evaluated are TAB, epidural blockade, local anesthetic infiltration etc. By these methods post-operative pain may be reduced and the development of chronic pain may be prevented.

Antihyperalgesic[2] drugs like NMDA antagonists and gabapentin interfere with the induction and maintenance of sensitization where post LSCS pain relief is important. Adequate pain relief will enhance mobility, decrease the risk of thromboembolism, lead to adequate baby bonding and breast feeding. Pain and anxiety leads to inadequate breast feeding.[3]

Transmission of pain[4] signals evoked by tissue damage leads to sensitization of the peripheral and central pain pathways. Pre- emptive analgesia is a treatment that is initiated before surgical procedure in order to decrease this sensitization. Owing to the protective effect on the nociceptive system, pre empotive analgesia has the potential to be more effective than a similar analgesic treatment. Theoretically immediate postoperative pain may be reduced,there by preventing the development of chronic pain.The only way to prevent sensitization of the nociceptive system might be to block completely any pain signal originating from the surgical wounds from the time of incision until final wound healing. NMDA antagonists and Gabapentin may interfere with induction and maintenance of central and peripheralsensitization.

Pain signals from the damaged tissue are not transmitted to the central nervous system through hard wired pathways. In contrast, nociceptive signals once initiated will launch a cascade of alteration in the somato sensory system including an increase in responsiveness of both the peripheral and central neurons.These alterations will increase the response to subsequent stimuli thus amplifying pain.[5,6,7,8]

[9,10,11]The term diclofenac is derived from its chemical name,dichloro2(2-(2,6phenyl amino phenyl acetic acid. In UK and USA it is supplied as sodium or potassium salt. IUPAC name is

2-(2 –(2.6 dichloride phenyl amino phenyl) acetic acid.It's chemical formula is ($C_{14}H_{11}$ $C1_2$ No_2.Molecular mass 296.148 gm /ml. The pharmacokinetic data[12] are as follows, Bioavailability 100% , protein binding more than 99%, metabolism hepatic, no active metabolite t½ 1.2 -2 Hrs and 35% Of the drug enters enterohepatic Circulation. Excretion mainly occurs through biliary route and 1% in urine

Diclofenac[13] is a phenyl acetic acid derivative which is a relatively nonselective cox inhibitor. It is one of most potent NSAIDS. It has analgesic, antipyretic andantiinflammatory properties, substantially greater than that of indomethacin and naproxen.Oral diclofenac has substantial first pass effect, only 50% is available systemically.

It is metabolized in liver by cytochrome P450 coenzyme of cyp 2c subfamily to 4-OH diclotenac the principal metabolite and otherhydroxylated forms after glucuronidation and sulfation.Diclofenac is available in dosage forms like tablets, intramuscular, intravenous, preparation, suppository and transdermal patch forms.

Mechanism of action of diclofenac[14] is by inhibition of cyclooxygenase, inhibition oflipoxygenase pathways and phospholipase A_2. It is the most potent analgesic NSAID on broad basis.

In this study, we use the dosage forms suppository and transdermal patch. Diclofenac suppository is avalibale in strengths of 12.5 mg , 50 mg and 100 mg. Maximum dose of suppository is 150 mg. Each strip has five diclofenacSuppositories have more rapid onset but slower rate of absorption than enteric coated tablets.

Since about half the active substrate is metabolized by first pass effect. Area under curve (AUC) following oral and rectal administration is also half as large as it is following equivalent parenteral dose.

Advantagesof suppositories are that there is no gastric irritation, the duration of action can be controlled with suitable solvent, it is useful particularly in geriatric and terminally ill patients.Advantages ofsuppository are that it can be administered by the patients themselves, good compliance , tolerance and rapid onset of action when compared to oral diclofenac.

Diclofenactrans dermal patch each with 75 cm^2 area contains the drug in the form of diclofenacdiethylamine.These patches deliver the contained drug at constant rate in to circulation via the stratum corneum of epidermis.

The drug is held in a reservoir between an occlusive leaking film and controlling micropore membrane

The trans dermal patch is available in strengths of 100 mg and 200 mg.

II. Materials And Methods

This study was conducted at SreeAvittomThirunal Hospital, the women and children wing of Medical College, Thiruvananthapuram during the period 2006-2008. After getting approval from the research and Ethical Committee of the hospital, 100 patients undergoing Lower Segment Caesarian Section under Lumbar subarachnoid (LSAB) block were studied by the prospective randomized clinical trial. Sample size[N] was calculated using the formula

$$N = \frac{2\sigma^2 \times f(\alpha,\beta)}{\delta^2}$$

σ = **std deviation**

δ = **effect size** α **5%** β **5%**

$$\text{Sample size (N)} = 100 \times \frac{}{\text{No of group}}$$

$$= 100 = 50 \text{ each}$$

Only those patients who satisfice following criteria like Lower Segment Caesarian Surgery patients undergoing surgery under spinal anaesthesia, Those between 18-30 years of age, Those having height between 155 cm to 175 cm, ASA grade I and ASA grade II patients Duration of surgery not beyond 90 minutes and Initial Spinal Sensory level above T_6 segment were selected.

Exclusion criteria In this study were Failed spinal anaesthesia, Inadequate spinal Sensory level, those with previous hypersensitivity to NSAIDS, patients with angioedema, urticaria and bronchial asthma, patients

having bleeding and coagulation disorders, patients with severe renal disease, congestive cardiac failure, severe preeclampsia and hepatic insufficiency, those patients having acid peptic disease, gastiritis, melena, those with history of proctitis and ulcerative colitis.

Study was conducted in both emergency and elective caesarian section cases. Thorough preanaestheticcheck 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.

Informed consent and consent for conducting the study were taken. All elective cases were fasted for a minimum of eight hours and for emergency cases high risk consent was taken.

All elective cases premedicated with Ranitidine 150mg and metoclopramide 10mg 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 50mg 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. Study, includes two groups of patients group(I)patch group. Group(II)- suppository group.

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

Pre-loaded with 250-500ml normal saline. Patient positioned in the left lateral position, with hipand 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 L_3-L_4 or L_4-5 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 + inj morphine 0.05 mg/kgwt 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 adjust so that patient was in supine position.

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 group (i) patients once surgery is over Diclofenac Sodium 100mg 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.

For the group(ii) suppository group clean the area around rectum with mild soap and warm water. Gently dry by patting. Detach one suppository (100mg strength) from the strip. Remove wrapper before inserting suppository by holding suppository up right and carefully peeling wrapper evenly down both sides of suppository. Avoid excessive handling as the suppository is designed to melt at body temperature. Position the patient flat on back or on one side with anal opening exposed. Gently insert the suppository well into rectum use finger tip to complete insertion. If necessary hold buttocks together for 30-60 seconds to keep suppository in place. Time of placement of suppository noted. Given instruction to avoid other analgesic drugs in the form of opioids or NSAIDS.

In the post operative period, 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 I/V incremental doses until patient is relieved of the pain in all these patients 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 all the patients

Duration of analgesia extends from the time of placement of transdermal patch or suppository, 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 were observed for occurrence of nausea,shivering, vomiting, excessive bleeding, itching etc.

Comparison of demographic profile

Table.1 Distribution of the sample patients according to weight

Weight kg	Patch		Suppository		χ^2	p
	Count	Percent	Count	Percent		
55-59	14	28.0	9	18.0	7.3	0.121
60-64	24	48.0	36	72.0		
65-69	12	24.0	5	10.0		
Average	61 ± 2.5		61.7 ± 2.1			

Fig..1 Comparison of sample patients according to mean weight

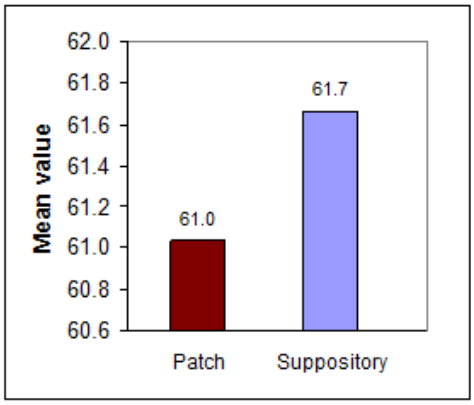


Table2. Distribution of the sample patients according to height

Height cm	Patch		Suppository		χ^2	p
	Count	Percent	Count	Percent		
156-160	32	64.0	30	60.0	6.49	0.166
161-164	10	20.0	12	24.0		
165+	8	16.0	8	16.0		
Average	161.5 ± 5.5		161.4 ± 4.7			

Fig2.. Comparison of the sample patients according to mean height

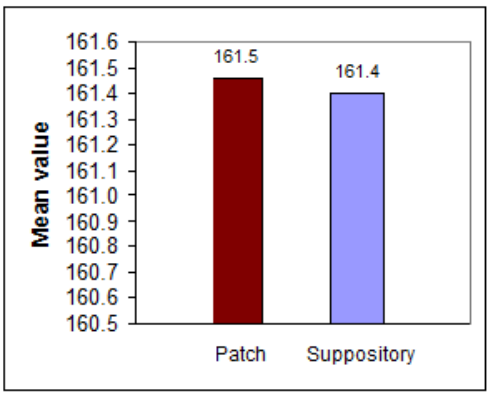
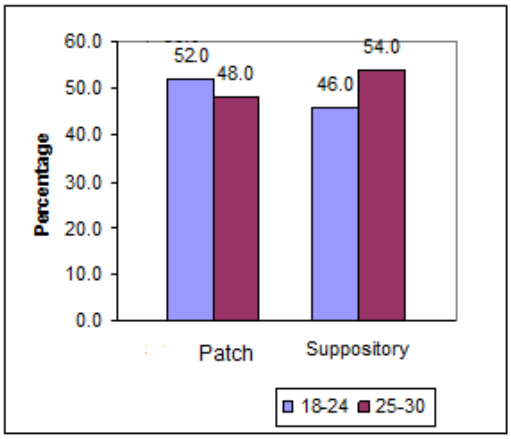


Table.3 Distribution of the sample patients according to age

Age yrs	Patch		Suppository		χ^2	p
	Count	Percent	Count	Percent		
18-24	26	52.0	23	46.0	1.01	0.602
25-30	24	48.0	27	54.0		

Fig.3 Distribution of the sample patients according to age



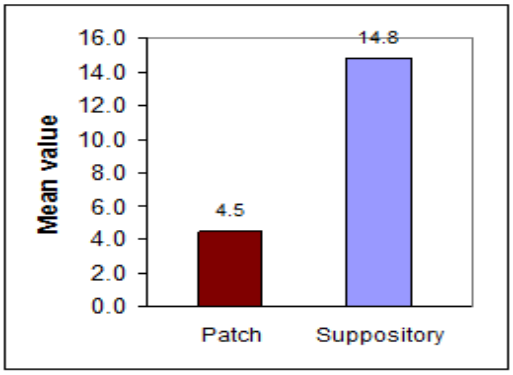
Demographic profile was found to be Insignificant as P value was more than .01

Table 5 Comparison of duration under Suppository and Patch

	Mean	SD	N	p
Suppository	14.8	1.1	50	0.000
Patch	4.5	1.0	50	

** : significant at 0.01 level

Fig4. compariison of duration under different treatments



Duration of analgesia provided by suppository was 14.8hrs compared to transdermal patch which provided duration of 4.5hrs. This shows that suppository was more effective.

III. Discussion

Pre emptive analgesia for caesarian section in Al najaf city conducted by Basimesh Al Ghazalietal showed that patients in whom lower segment caesarean section is done under lumber subarachnoid block and multimodal analgesia with acetaminophen and fentanyl post-delivery showed lowest opioid analgesic requirement,in Comparison With Patients who had surgery under general anesthesia and local infiltration anesthesia.

The advent of pain prevention was instituted in to clinical practice by crile in 1913 and later developed by wall and woolf.Women with acute post-partum pain had 2.5 fold risk of persistent pain and 3 fold increased risk of postpartum depression.

The various methods of post caesarian analgesia includes wound infiltration with local anaesthetics, opioids, ketamine, gabapentin andileoinguinalilehypogastric nerve block (II-IH NB). Administration of opioids is the gold standard method which leads to adverse effects like respiratory depression,[15] inadequate breast feeding and hypoglycemia in the neonate. It has led to the mandatory induction of non-opioid analgesia in post section analgesia regimen.Opioids like morphine and pethidine are the ones mostly used in LSCS patients.

skin has a stratum corneum[16] containing keratins , large amounts of fat ,wax and cholesterol.Diclofenac sodium[17] is contained in a pressure sensitive adhesive material layer in combination with organic acids in transdermal patch.Diclofenac sodium can be converted in to free based diclofenac in pressure

sensitive adhesive material layer.Diclofenac sodium is converted free based diclofenac having high oleophilicity[18].

Pre-emptive analgesia is the administration of an analgesic before a noxious painful stimulus in order to ablate the altered processing of afferent input which amplifies post-operative pain.Pre-emptive analgesia should prevent the establishment of central sensitization caused by incisional injuries.

Other novel methods of transdermal drug delivery are iontophoresis, ultrasound, microneedles, electroporesis, laser, ablation, magnetophoresis, use of hybrid medthods, liposomes and nanocarriers. Iontophoresis is by application of low intensity electric current[19]

Use of ultrasonic technique to transport drugs across the skin is termed as phonophoresis[20]

1% Diclofenac epidermal patch[21] provides pain relief in sprains, sports injuries and osteoarthritis.Transdermal NSAID was found to be more superior when compared to oral NSAID in providing analgesia for osteoarthritis[21,22]

The only method to ablate central sensitization is to completely block any pain and afferent signals from the incisional wound from the time of incision to final wound healing. By the application of analgesia pain will either subside or will be prevented prior to the inciting painful stimulus by preventing central sensitization and subsequently decreasing the need for postoperative analgesia.Because of this protective effect on the nociceptive system, preemptive analgesia is more effective than similar analgesia initiated after surgery

NSAIDS and preemptive analgesia was studied using 20 trial odontological, abdominal and orthopedic procedures.Some aspects of post-operative pain control are improved by pre – emptive treatment in four of the twenty trials in the but no improvement was noted in remaining trials.

Intravenous opioids in eight trails compared pre incisional with postincisional administration of various opioids.It was concluded that no overall improvement in postoperative pain control was demonstrated after pre-emptive administration of systemic opioids

N methyl D aspartame (NMDA) antagonists like ketamine at metaanalysis showed that pre-emptive ketamine didn't produce any improvement in post-operative pain control

In my study pre-emptive analgesia is administered at the end of surgery before vaning of the lumbar subarachnoid block.Diclofenac suppository 100mgm was more effective compared to the diclofenac100mgm Trans dermal patch, both in quality and duration of analgesia. Diclofenac suppository induced analgesia lasted for more than 14.8 hours compared to the diciofenac transdermal patch with which post-operative analgesia lasted only for four hours. VAS score was less for diclofenac suppository. Rescue analgesic dose needed was also less for the suppository group.Hence the administration of post incisional diclofenac suppository at the end of surgery is a cost effective means of extending the pre-emptive analgesia in continuation with the central neuroaxial blockade which was administered preincisional.

In this study, the rescue analgesia was given after hours and if we administer the pre-emptive analgesia continually in the form of diclofenac suppository the onset of post-operative pain can be further delayed thereby it proves that the administration of centrineuraxial blockade before incision can extend the pre-emptive analgesia to the post operative period via simple administration of suppository.

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