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Original research article

Transdermal patches of buprenorphine (10mg) and diclofenac (200mg) for of post-operative analgesia: adverse effects and patient satisfaction

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Abstract
Buprenorphine is a highly lipophilic semisynthetic opioid.it is derived from thebaine, a morphine opioid. Buprenorphine is a partial agonist at μ opioid receptors which has high affinity but moderate intrinsic activity. Buprenorphine is also an antagonist at kappa-opioid receptors and delta -opioid receptors, and a partial agonist at ORL-1 (nociceptin) receptors. Following ethics committee approval, informed written consent was obtained from the patients. Detailed pre-anaesthetic evaluation was done. Demographic (age, gender), morphological (height, weight) and vital parameters were recorded. In our study 7 patients in Buprenorphine group had nausea/vomiting and one patient was drowsy but arousable whereas in Diclofenac group 4 patients had nausea and none of the patients were sedated during the entire study period.
Keywords: Transdermal patches, buprenorphine, diclofenac

Introduction
Transdermal drug delivery system, often known as patches, is a non-invasive way of delivering medications across the dermis or skin surface which can deliver a drug at a predetermined rate across the skin to receive a local or systemic effect.In the year 1979, first transdermal therapeutic system was developed by M/s Alza Corporation. The patch was launched to the market containing scopolamine intended for motion sickness. The success of scopolamine patch put forth many innovative designs for transdermal delivery which are being launched commercially. A decade later the success of nicotine patch brought in more awareness and usage of transdermal patch[1].
As the transdermal patches are applied on the skin and the drug is absorbed systemically through the skin, the anatomy of skin is of vital.
The transdermal system of Buprenorphine provides systemic delivery of buprenorphine, a mu opioid partial agonist analgesic, continuously for 7 days. The chemical name of buprenorphine is 6,14-ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)- α-(1,1-dimethylethyl)-4, 5-epoxy-18, 19-dihydro-3-hydroxy-6-methoxy-α-methyl-, [5α, 7α, (S)][2].
Buprenorphine is a highly lipophilic semisynthetic opioid.it is derived from thebaine, a morphine opioid. Buprenorphine is a partial agonist at μ opioid receptors which has high affinity but moderate intrinsic activity. Buprenorphine is also an antagonist at kappa-opioid receptors and delta -opioid receptors, and a partial agonist at ORL-1 (nociceptin) receptors[3].
Diclofenac is the one of the most commonly prescribed NSAID. It is commercially available as oral, injections, suppositories, topical and transdermal preparations.The transdermal system of Diclofenac provides systemic delivery of Diclofenac for twenty-four hours, which is a phenyl acetic acid derivative having anti-inflammatory, anti-pyretic and analgesic activity.
Diclofenac Diethylamine is a non-opioid analgesic chemically designated as 2-[(2,6dichlorophenyl) amino] benzeneacetic acid, (2-(pyrrolidin-1-yl) ethanol salt, with a molecular formula of C20H24Cl2N2O3

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(molecular weight 411.3), an N-octanol/water partition coefficient of 8 at pH 8.5 [4].

Methodology

A total of 60 patients were enrolled for the study with the following inclusion and exclusion criteria.

Inclusion criteria

1. ASA 1 and 2.
2. Age between 20-60 years of either sex.
3. Weight up to 80 kg.
4. Patients posted for surgery under general anaesthesia.

Exclusion criteria

1. Patients with
2. Known hypersensitivity to any drugs
3. Pregnancy
4. Opioid dependence
5. Narcotic withdrawal and conditions in which the respiratory center and its functionare severely impaired
6. ASA 3 and 4

Following ethics committee approval, informed written consent was obtained from the patients. Detailed pre-anaesthetic evaluation was done. Demographic (age, gender), morphological (height, weight) and vital parameters were recorded. Patients fulfilling the essential criteria undergoing the following surgeries-laparoscopic cholecystectomy, total or hemi thyroidectomy, laparotomy, other laparoscopic assisted surgeries under general anaesthesia were selected. Patients were randomly divided into two groups of 30 patients each using sealed envelope method and were applied transdermal patches as follows-

Group B: Buprenorphine (TDB) (10 mg),

Group D: Diclofenac (TDD) (200 mg).

Results

The mean Age was 39.6 ±9.3 years in group B and 40.0 ± 8.9 years in group D. The mean Height was 156.8 ±7.3 cm and 154.3 ± 5.0 in group B and group D respectively. The mean Weight was 61.4± 8.5 kg and 58.8±9.5 kg in group B and group D respectively. The mean BMI 25.0 ± 3.1 in group B and 24.7± 2.3 in group D.These are not statistically significant.

Table 1: Age profile

Parameters	Group B		Group D	
	Mean	±sd	Mean	±sd
Age(yrs)	39.6	9.3	40.0	8.9

Table 2: Distribution of weight& height

Parameters	Group B		Group D	
	Mean	±sd	Mean	±sd
Weight(kg)	61.4	8.5	58.8	5.5
Height(cm)	156.8	7.3	154.3	5.0

Table 3: Distribution of BMI

Parameters	group B		group D	
	mean	±sd	mean	±sd
bmi(kg/m2)	25.0	3.1	24.7	2.3

Group B had 13 males and 17 females. Group D had 9 males and 21 females. This is statistically not significant.

Table 4: Gender profile

Sex	Group B		Group D	
	N	%	N	%
Male	13	43.3	9	30.0
Female	17	56.7	21	70.0
Total	30	100.0	30	100.0

5 Patientsin group B and17 patients in group D felt excellent pain relief. 19 patients in group B and 13 patients in group D gad moderate pain relief.6 patients experienced poor quality of pain relief whereas none

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of the patients had poor pain relief in group D. Overall, the quality of pain relief was better in Diclofenac group than Buprenorphine group.

Table 5: Quality of pain relief seen

Quality of pain relief	Group B		Group D		P value
	N	%	N	%	
Excellent	5	16.7%	17	56.7%	0.001*
Moderate	19	63.3%	13	43.3%	
Poor	6	20.0%	0	0.0%	
Total	30	100.0%	30	100.0%	

Note: *Significant at 5% level of significance (p<0.05)

In our study7 patients in Buprenorphine group had nausea/vomiting and one patient was drowsy but arousable whereas in Diclofenac group 4 patients had nausea and none of the patients were sedated during the entire study period.

Table 6: Adverse effects and complications

Adverse reactions		Group B		Group D		P value
		N	%	N	%	
30 minutes	Nausea	5	16.7	3	10.0	0.554
	Sedation rsc-2	1	3.3	0	0.0	
6 hours	Nausea	2	6.7	1	3.3	0.554
18 hours		0	0.0	0	0.0	-
Day 1		0	0.0	0	0.0	-
Day 2		0	0.0	0	0.0	-
Day 3		0	0.0	0	0.0	-
Day 4		0	0.0	0	0.0	-

Table 7: Adverse effects and complications

	Adverse reactions	Pre- operative	30 minutes	6 hours	18 hours	Day 1	Day 2	Day 3	Day 4
Group B	Sedation	0	1	0	0	0	0	0	0
	Nausea	0	5	2	0	0	0	0	0
Group D	Sedation	0	0	0	0	0	0	0	0
	Nausea	0	3	1	0	0	0	0	0

Discussion

The problems of post- operative pain include hypoxia, breathlessness, metabolic acidosis, metabolic alkalosis, psychological breakdown, increased hospital stay and morbidity.The higher incidence of complications, such as myocardial infarction, arrhythmias and pneumonitis can occur when pain is poorly relieved.The benefits of post- operative pain relief is important as it facilitates overall recovery, improve patient satisfaction, reduce health care cost, decrease morbidity, improve functional outcome, quality of life. And conversion to chronic post- surgical pain.The methods of pain relief are (NSAIDs), Sublingual and intravenous (IV) opioids Parenteral NMDA receptor antagonists, Local anaesthetics (LA) for neuraxial administration, peripheral blocks, wound infiltrations, and intraperitoneal instillations, SystemicAnticonvulsant - GABA (gamma-amino butyric acid) analogues. Among these, opioids and NSAIDS are the most commonly used agents [5]

Traditionally opioids have been the main-stay of acute postoperative pain management. They provide excellent analgesia. However, they are not suitable for treatment of somatic pain due to peripheral tissue injury. They are also associated with adverse outcomes like respiratory depressions, cardiovascular depressions, post-operative nausea and vomiting, impairment of bowel function, urinary retention, pruritus etc.Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used medications in the world because of their demonstrated efficacy in reducing pain and inflammation. Their efficacy has been documented in a number of clinical disorders including osteo- arthritis, rheumatoid arthritis, ankylosing spondylitis, gout, dysmenorrhea, dental pain and headache. The basic mode of action is inhibition of pro-inflammatory enzyme cyclo-oxygenase(COX). Although effective at relieving pain and inflammation, systemically administered NSAIDs are associated with a significant risk of serious gastrointestinal adverse events and potential cardiovascular side effects and variation in pain control levels with peak to trough fluctuations and gastro- intestinal complications [6].

Analgesics can be administered by various routes, including oral, parenteral, and inhalational and transdermal.Oral route has the risk of first pass metabolism and loss of substantial quantities of the drug before it is absorbed systemically.Parenteral administration of drugs can be extremely painful and sudden increase in drug concentration in the plasma could lead to certain adverse effects[7].

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As the understanding of pain pathophysiology and treatment is increasing, new routes of drug delivery are being discovered with the objective of attempting to block pain at peripheral sites, with maximum active drug and minimal systemic effects. Topical (transdermal) preparations are the result of such exploration, which are expected to be free of the drawbacks of oral and parenteral routes.

The transdermal patches offer several advantages over the oral routes such as bypassing first pass metabolism, accurate drug doses, and slow controlled absorption, constant plasma concentration which is maintained for a longer duration, no patient dependence for drug doses, no gastric discomfort, and flexibility of terminating the drug administration by simply removing the patch from the skin. Since TDDS avoids the first pass effect, the therapeutic value of many drugs having poor bioavailability (like Buprenorphine) could be enhanced. Moreover, frequency of the dosing can be reduced for drugs having shorter half-lives (t1/2).

Buprenorphine is the most popular opioid being used by transdermal route, owing to its favourable physicochemical properties such as low molecular weight, high lipophilicity and high affinity for μ receptors make it well suited for transdermal delivery. Systemically, it is 75- 100 times more potent than Morphinebut causesless respiratory depression and has good safety profile compared with other opioid analgesics in last 30 years. Transdermal buprenorphine has been used in the management of chronic pain (cancer and non- malignant pain).There are not many studies in acute post- operative pain. Similarly, Diclofenac is also very popular NSAID being used as transdermal patch for acute pain relief owing to safe and effective pharmacological profile. Present study is undertaken to compare their relative efficacy as transdermal patches in the setting of acute post- operative pain [8].

The single application of transdermal patch of Buprenorphine acts for seven days due to slow release of Buprenorphine drug from both the patch and the μ receptors. So only one patch will be adequate for the peri- operative period. The Diclofenac patch has quick onset of action and single application acts for twenty-four hours. Hence, it has to be repeated every 24 hours peri- operatively.The transdermal Buprenorphine patch has to be applied at least twenty four hours before surgery as the time required for Buprenorphine drug to reach effective plasma concentration is twelve to twenty four hours. Therefore, in our series Buprenorphine patch was applied on the day before surgery, similar to studies done by Niyogi*et al* (2017), Desai *et al* (2017)and Rajan *et al* (2019). For uniformity sake and comparative study, both transdermal patches of Buprenorphine and Diclofenac were applied twenty-four hours before surgery in our series.In the study conducted by Yadav *et al* (2019), the transdermal Buprenorphine patch was applied 12 hours before and Kumar *et al* (2016)[12], the transdermal Buprenorphine patch was applied the pre-operative night. Rao *et al* (2016) applied transdermal Diclofenac patch after giving spinal anaesthesia. Bachalli*et al* (2009) applied the transdermal patch 30 minutes after extraction of mandibular impacted third molars under inferior alveolar nerve block.Samal*et al* (2013) have used Diclofenac patch after the surgical procedure (laparoscopic, gynaecological and orthopaedic surgeries) in patients undergoing general/spinal anaesthesia**.** Bhargava *et al* (2015) also applied the transdermal Diclofenac patch one hour before the end of surgery [9].

Buprenorphine is available as patches 5, 10 and 20 mg. Each transdermal patch of Buprenorphine usually contains 5mg of Buprenorphine in 6.25 sq. cm which releases 5 mcg/hr. Each 10 mg patch which is 12.5 sq. cm releases 10 mcg/hr.Total dose per day should not exceed 20 mcg per hour. As per the monogram by the manufacturers pharmacokinetically, the minimum titration interval for Buprenorphine is 72 hours, to reach steady state levels[10].

Diclofenac is available as 50sq cm (100 mg) and 75 sq. cm (200mg). The patch achieves plasma levels of 20- 50 ng/ ml which is sustained for a long time but is compared to the oral route.Likar (2006) states that owing to prolonged onset time of Buprenorphine and its maintenance at therapeutic plasma concentrations over a period of one week, it may be more useful for pre-emptive analgesia to reduce post- operative pain than managing acute pain [11].

Pre-emptive analgesia involves pre- operative administration of analgesics that helps to reduce the consequences of afferent nociceptive neurotransmission before or during surgery and thereby decreasing postoperative pain. Preventive analgesia involves prevention of central sensitization by blocking the neural transmission of all noxious perioperative stimuli arising from the time of incision to till wound healing.It provides pain relief better than the same analgesic used after the painful stimuli. Galer*et al* states that in post- operative setting, Diclofenac works better in anticipation of pain and not after patient experiences pain in the post- operative period. Shat *et al*. showed that diclofenac sodium is more effective when given pre-emptively. Safinazet at states that both intramuscular and patch of Diclofenac were equally effective in prevention of post- operative pain. In our series, both drug patches were applied twenty- four hours before surgery. Hence, they were expected to produce adequate pre-emptive analgesia [12].

Nerve blocks and regional techniques also may to certain extent minimize or prevent peripheral sensitization component after surgery. Also, analgesics such as ketamine, morphine or nitrous oxide, given to patients prior to surgery, may act pre-emptively and prevent significant central sensitization.

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Conclusion

6 patients in Buprenorphine group had nausea/vomiting and one patient was drowsy but arousable whereas in Diclofenac group 4 patients had nausea and none of the patients were sedated during the entire study period. The quality of pain relief was better in Diclofenac group than Buprenorphine group (p 0.001). No significant adverse effects were noted in both the study groups.

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