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EFFECTS OF TRANSDERMAL BUPRENORPHINE AND DICLOFENAC FOR POST-OPERATIVE PAIN RELIEF IN PERCUTANEOUS NEPHRO-LITHOTOMY (PCNL) SURGERY: A PROSPECTIVE RANDOMIZED CONTROL TRIAL

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ABSTRACT

BACKGROUND: A transdermal buprenorphine and diclofenac sodium formulation has been utilized for the management of chronic pain and other purposes. Transdermal patch application has resulted in better pain management but are also associated with many side-effects including local irritation and allergy. Their role in post-operative pain management is also being studied. A study to look into their effectiveness was warranted for PCNL surgeries.

AIMS: The aim of this study was to compare the analgesic efficacy of transdermal buprenorphine and diclofenac patch for post-operative pain following PCNL surgery. We also aimed to determine the hemodynamic changes, patient's satisfaction and adverse reactions following application of these transdermal patches.

MATERIAL AND METHODS/DESIGN: A prospective, randomized control trial involving 60 patients into 2 groups. Group A included 30 patients on whom transdermal buprenorphine 10mg patch was used and group B had 30 patients where diclofenac sodium 200 mg patch was used. We recorded pain with numeric rating scale and patient satisfaction. We also documented any side-effects and hemodynamic changes. Statistical analysis done with SPSS 23

RESULTS: There was no difference in baseline parameters of both groups. Pain score was 1.53±0.68 for group A compared to 2.23±1.14 for group B at 8 hours (p =0.005) Patient satisfaction was excellent in 87% for group A and 47% for group B (p =0.003). No significant difference was found in side-effects among both groups.

CONCLUSION: Application of transdermal buprenorphine for up to 8 hours appears to be a promising option for the management of post-operative pain following PCNL procedure.

KEYWORDS : Transdermal patch, Buprenorphine, Diclofenac, PCNL, Post-operative analgesia.

INTRODUCTION:

Percutaneous Nephrolithotomy (PCNL) is an important stone removal surgery which requires surgical as well as anaesthetic expertise, for the prevention and management of postoperative pain and complications.

Pain is primarily caused by puncture and dilatation of PCNL tract with resultant tissue damage and adequate pain control is related to better postoperative experience of patient. Pain management strategies includes intravenous (IV), oral or transdermal non- steroidal anti-inflammatory drugs (NSAIDS), opioids, local injection of anaesthetic agent like lignocaine and epidural analgesia. Opioid analgesics are related to side-effects like poor mental concentration, constipation, urinary retention, nausea, vomiting, itching, hemodynamic and respiratory complications as compared to NSAIDS. Oral preparations are of less use in immediate perioperative period, as many of these drugs have high first pass metabolism and sometimes patient's compliance becomes huge hurdle. Intramuscular preparations are irritating and painful at the site of injection as it can cause skin, subcutaneous and muscle necrosis, Nicolau syndrome and abscess formation.[1]

Novel routes are being discovered to block pain at peripheral sites with better understanding of pain pathophysiology. Delivering active agents via topical application to the healthy skin either for localized or systemic therapy is the principle of transdermal patches. Constant blood levels, avoidance of dose dumping, better patient compliance and termination of the therapy are the advantages of this, over previous drug delivery systems as it mimics the slow iv infusion without its potential hazards.[2] Delivery Systems are defined as self-contained, discrete dosage forms which are also known as patches.[3,4] When patches are applied to the intact skin, they deliver the drug through the skin at a controlled rate to the systemic circulation.[5,6] Transdermal patches are supposed to reduce first pass metabolism and side effects of drugs. They have expanded adaptability in drug organization by fixed expulsion and easy application. Nonetheless, there are few impediments also for example local irritation, trouble in conveying hydrophilic medications, higher cost of medicines and long retention. Currently transdermal delivery is one of the most promising methods for drug application. It reduces the load that the oral route commonly places on the digestive tract and liver. It enhances patient compliances and minimizes harmful side effects of a drug caused from temporary over-dose and is convenient in trans-dermally delivered drugs that require less frequent application.[7]

A transdermal buprenorphine formulation has been developed and has been utilized for the management of chronic pain or cancer pain.[8] Buprenorphine, a derivative of the opium alkaloid thebaine, is a more potent and longer lasting analgesic than morphine. Its dissociation from opioid receptor binding is slow which accounts for its longer duration of action compared to morphine. However, there is limited clinical experience of utility of transdermal buprenorphine patch in postoperative pain.[9]

Diclofenac sodium, an aryl acetic acid derivative, is the commonly employed NSAID either as a sole agent or in combination with other NSAIDs.[10] It is a non-selective cyclo-oxygenase inhibitor which acts by inhibition of the pro-Inflammatory enzyme cyclo-oxygenase. It can be delivered through the skin as a transdermal patch. Transdermal route allows a controlled delivery of the drug into the circulation.[11] We aimed for comparison of transdermal diclofenac and buprenorphine patches after PCNL surgery in terms of pain relief, side effects and patient satisfaction.

Materials And Methodology:

This was a prospective randomised control trial involving 60 patients undergoing PCNL. Initially a total of 65 patients were assessed for study but after exclusion criteria 60 patients were selected. We included all patients from 18-60 years of age. Pregnant women, mentally confused or mentally handicapped patients, patients with history of allergy to drug or with neuropathies or nerve injuries were

excluded from study. All the patients were randomly allocated to either Buprenorphine patch group or Diclofenac sodium patch group. The randomisation was done by using computer generated method. Ethical clearance was obtained from institutional ethical clearance committee with number IE-104/2019. Study was in line with Helsinki declaration as revised in 2000. A detailed and well-informed written consent was obtained from all patients. Group A included 30 patients who received Buprenorphine patch and Group B had 30 patients who received Diclofenac sodium patch after PCNL surgery. Transdermal patch was applied to skin once in a day. The patch was not used if these are cut, damaged, or changed in any way. After cleaning and drying the area completely, patch was applied four hours prior to the surgery. Oils, soaps and emulsions were not used. After opening pouch, patch was pressed on skin for at-least 15 seconds, preferably at a non-hairy region. If any difficulty arises in sticking of edges, first aid tape was used for sticking. After finishing the application of patch, hands were washed. Date and time of application of patch was noted. If a patch falls of before its removal time, disposal of the patch was done properly and a new patch was applied at a different area of skin. Tablet Paracetamol 500 mg orally was used as rescue analgesia whenever patient required, while on patch. Patients and primary investigator were kept blinded for analgesia patch received. We assessed pain with numeric rating scale (NRS) which ranges from 0-10. NRS is a self-reported scale which depends on daily activities of patient. NRS was recorded at 0,2,4,6 and 8 hours after surgery and graded on scale as follows:

0: No pain
1-3: Mild pain
4-6: Moderate pain
7-10: Severe pain

Patient satisfaction was also evaluated in the wake of applying the patch on a 4 point scale as excellent, good, fair and poor.

A. Excellent: Agony Is Completely Settled Or Reduced ≥75%.
B. Good: Reduction Of Agony Is By 50% - 74%.
C. Fair: Reduction Of Agony Is By 25% - 49%.
D. Poor: Reduction Of Agony Is ≤25% Or There Is An Increase In Agony.

We also documented various side-effects and hemodynamic parameters in both groups. Continuous variables were expressed as the mean ± SD and categorical variables as a percentage. Chi-square tests and students unpaired t test were used. All statistical calculations were done using SPSS 23(Statistical Package for the Social Science). A probability value (p-value) less than 0.05 was considered statistically significant.

RESULTS:

Baseline characteristics were compared and there were no significant difference found in age, gender, weight, ASA status and Mallampatti grade between both groups. (Table 1)

Table 1: Baseline Characteristics Among Buprenorphine And Diclofenac Group.

S. no	Parameter	Buprenorphine group (n=30)	Diclofenac sodium group (n=30)	P value
1.	Age (years) (Mean±SD)	39.50±10	37.53±9.29	0.433
2.	Gender	Male: 23 (77%)	Male: 19 (63%)	0.260
		Female: 7 (23%)	Female: 11 (37%)	
3.	Weight	75.70±10.4	73.93±10.1	0.507
4.	ASA status	ASA1: 19 (63%)	ASA1: 22 (73%)	0.405
		ASA2: 11 (37%)	ASA2: 8 (27%)	
5.	Mallampatti grade	Grade 1: 16 (53%)	Grade 1: 14 (47%)	0.606
		Grade 2: 14 (47%)	Grade 2: 16 (53%)	
ASA: American society of anaesthesia				

We analysed pain score at 0,2,4,6 and 8 hours after surgery with NRS and found that buprenorphine patch was associated with lesser pain at 8 hours and the difference was statistically significant. (Table 2)

Table 2: Pain Score With Numeric Rating Scale (nrs) Among Both Groups.

S. no	NRS pain score	Buprenorphine (n=30) (Mean±SD)	Diclofenac sodium (n=30) (Mean±SD)	P value
1.	0 hours	5.23±1.04	5.27±0.87	0.893
2.	2 hours	4.57±1.17	4.50±1.01	0.814
3.	4 hours	3.93±1.11	4.03±1	0.715
4.	6 hours	2.00±0.74	2.37±1.38	0.204
5.	8 hours	1.53±0.68	2.23±1.14	***0.005***

We also compared patient satisfaction for pain relief on 4 point scale and found that buprenorphine group had better satisfaction rate (p value- 0.003). (Table 3) None of patient had poor satisfaction in both the groups. Also none of the patients required rescue analgesia in our study.

Table 3: Comparison Of Patient Satisfaction For Pain Relief Among Both Groups

S.no	Parameter	Buprenorphine group (n=30)	Diclofenac sodium group (n=30)	P value
1.	Excellent	26 (87%)	14 (47%)	***0.003***
2.	Good	4 (13%)	12 (40%)	
3.	Fair	0	4 (13%)	
4.	Poor	0	0	

Similarly, we compared side- effects in both groups and found no significant difference in vomiting, dizziness and skin irritation. We also compared heart rate and mean arterial pressure at 0,2,4,6 and 8 hours and found that heart rate was significantly lower in buprenorphine group than diclofenac at 6 and 8 hours. There was no significant difference seen in mean arterial pressure between 2 groups. (Table 4)

Table 4: Comparison Of Heart Rate And Mean Arterial Pressure Among Both Groups

S.no	Parameter	Time (hours)	Buprenorphine group (n=30)	Diclofenac sodium group (n=30)	P value
1.	Heart rate (beats/min) (Mean±SD)	0	88.70±11.19	90.27±14.59	0.642
		2	84.97±12.91	89.10±14.54	0.249
		4	83.10±12.29	88.00±15.51	0.180
		6	82.50±13.85	90.60±15.41	***0.036***
		8	80.77±14.35	89.57±15.66	***0.027***
2.	Mean arterial pressure (mmhg) (Mean±SD)	0	102.89±6.30	100.10±9.03	0.170
		2	94.65±8.86	95.65±10.26	0.688
		4	90.80±11.7	92.03±11.24	0.681
		6	87.21±12.5	91.58±10.55	0.149
		8	86.62±11.45	91.05±8.51	0.095

DISCUSSION:

Buprenorphine is an opioid analgesic with partial agonist activity at the mu-opioid receptor and antagonist activity at the kappa-opioid receptor, with high binding affinity at both sites. [12,13] In recent years, it has been known that buprenorphine has no ceiling effect on analgesia, making it a useful agent in the management of acute pain. The analgesia provided by buprenorphine was comparable to morphine beginning from 1 hour to 48 hours after operation.[14] In addition to this, buprenorphine administered in the emergency setting was reported as equivalent to morphine for the treatment of acute pain.[15] The injectable formulation of the drug requires skilled administration that may be inconvenient and provide a bolus effect that may be poorly tolerated, particularly in the elderly.[16]

We found in our study that post-operative pain was significantly low with buprenorphine transdermal patch at 8 hours compared to diclofenac patch. Also, patient satisfaction was higher with buprenorphine patch. Kumar et al [17] in their study found that buprenorphine (20mg) transdermal patch provided remarkable pain relief compared to buprenorphine (10mg) and placebo patch in postoperative period after abdominal surgeries. Similar study was done by Tang I et al[18] where buprenorphine patch, parecoxib intravenous injection and oral celecoxib were used for postoperative analgesia in patients undergoing lumbar discectomy and pain was measured using visual analogue score (VAS). They found a significant decrease in pain by buprenorphine transdermal patch compared to other arms. Xu et al[19] also studied efficacy on perioperative analgesia with buprenorphine patch, flurbiprofen axetil intravenous injection and oral celecoxib for hallus valgus surgery and buprenorphine patch was found to have better analgesic effect than other groups, measuring pain using VAS. Also, buprenorphine patch provided better satisfaction rate. A study done by lee et al[20] on efficacy and safety of buprenorphine patch compared with oral tramadol/ paracetamol for post-operative pain after spinal surgery. They measured intensity of

pain using NRS and found a significant decrease in pain with buprenorphine patch as time progress with NRS value from 5.04 ± 0.82 to 2.49 ± 1.40 (p <0.001). In a study done by krishna et al[21] using transdermal diclofenac patch 100mg for post-operative pain relief, found that intensity of pain decreased as time increased. In our study, diclofenac patch also decreased pain over time but it had a less significant impact on pain relief compared to buprenorphine group.

Though widely used, diclofenac is not an ideal choice for postoperative pain relief because of its potential complications, particularly in elderly and renal compromised patients. It is also preferably avoided in stomach and duodenal surgery.[22] By contrast, avoidance of multiple injections, prolonged steady-state plasma concentration, and central desensitization would be potential advantages of buprenorphine patch in the context of postoperative pain relief.

Our study also showed that patient who received buprenorphine patch for analgesia had more fall in heart rate compared to diclofenac patch at 6 and 8 hours but remained in within normal clinical range. We did not find any difference in mean arterial pressure among 2 groups. Another study done by Niyogi et al[23] showed that by using buprenorphine transdermal patch, heart rate and blood pressure were significantly reduced. Similarly, Kumar et al[17] showed that heart rate and blood pressure were significantly reduced with buprenorphine 20mg compared to buprenorphine 10 mg and placebo group.

In our study, 7% patients experienced nausea and vomiting, 3% patients experienced skin irritation and no patients experienced dizziness in buprenorphine patch group whereas,13% patients experienced nausea and vomiting,10% patients experienced dizziness and 7% patients experienced irritation in diclofenac patch group. Murphy et al[24] had concluded that, 35.6% of transdermal buprenorphine treated patients and 25.5% of placebo recipients had local skin reactions, mainly pruritus and/erythema but many studies suggest that local skin tolerability is not a limiting factor with transdermal buprenorphine treatment, as local skin symptoms that were detectable in roughly one third of patients, were typically mild or moderate, and generally subsided within a day after patch removal.[25] Overall buprenorphine transdermal patch has good analgesic effect, better patient satisfaction and lesser side effects as compared with diclofenac patch.

Our study is commendable as we performed a randomised trial with only single type of surgery for post-operative analgesia. Also, patients were blinded about their allotted group. Limitations of our study include a comparatively smaller sample size and non-blinding of investigators. Still, we were successful in demonstrating that buprenorphine patch was better in pain relief than diclofenac without any significant increase in complications.

CONCLUSION:

Buprenorphine transdermal patch is superior to diclofenac patch for post-operative analgesia after 6 hours and provide better patient satisfaction rate. Also, buprenorphine patch is not associated with any increased complication rate.

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