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Original Research Paper

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COMPARITIVE EVALUATION OF POSTOPERATIVE ANALGESIC EFFICACY OF TRANSDERMAL BUPRENORPHINE AND EPIDURAL INFUSION

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ABSTRACT

Background and Aims: Renal surgeries are responsible for moderate to severe postoperative pain which may cause further discomfort and if persistent may ultimately lead to chronic pain .Efficacious control of postoperative pain is a major challenge to treating surgeon and attending anaesthesiologist .Studies about the use of transdermal buprenorphine patches in postoperative analgesia are few and have contradictory results which could be because the studies were performed in different type of surgeries which can influence the degree of pain perceived. Though epidural analgesia is the gold standard but since it is invasive and has risk of side effects like hypotension, infection ,motor blockade etc. So we conducted a study to evaluate the efficacy of transdermal buprenorphine 10 mg patch with continuous epidural infusion for postoperative analgesia following renal surgeries. **Methods:** The study was a single centre, randomized control trial for one year. Patients were allocated into 2 equal groups of 20 each using computer generated random sequence of numbers .In one group of patients, a transdermal buprenorphine patch 10 mg was applied 20-24 hr at the time of pre anaesthetic check up, in other group of patients an epidural catheter was placed at the day of surgery under local anaesthesia at 12-13 level .Efficacy of pain was checked using numeric rating scale with 0 being no pain and 10 being worst pain and two groups were compared at 30 mins then 1hr post surgery for 6hrs then 2 hourly till 24 hrs. Numeric rating score of 4 or more was given rescue analgesia in form of fentanyl 1 mcgkghr to max of 2 mcgkghr. Rescue analgesic consumption if required was documented .Results :Higher scores on mean NRS were recorded in buprenorphine group as compared to continuous epidural group which showed that transdermal buprenorphine didn't provide adequate analgesia as compared to epidural infusion. On statistical analysis significant difference was observed between the two groups at all time periods which showed that continuous epidural infusion was much better than buprenorphine patch throughout. **Conclusion :** Though continuous epidural infusion is more effective for postoperative analgesia, transdermal buprenorphine patch can be used particularly in the setting where pain may last for several days. However there is need for exploring further observation in other surgeries also as being non invasive it can be used as in cases where contraindication to placement of epidural catheter exists.

KEYWORDS : Buprenorphine, Transdermal Patch, Epidural Infusions, Postoperative Analgesia, Chronic Pain

INTRODUCTION

Acute pain after surgery is a predictable, physiological response to tissue damage. Patients are usually prepared for some degree of pain or discomfort but expect that it will pass. However, up to one third of patients undergoing common surgical procedures report persistent or intermittent pain of varying severity at one year post operatively. Chronic pain is difficult and costly to treat, with wider costs associated with increased health service use as well as reduced quality of life and economic productivity. The burden of disease from chronic post surgical pain is potentially high if we consider the volume of surgical procedures performed annually.

Renal surgeries are associated with moderate to severe postoperative pain which can cause further discomfort and if persistent, may lead to chronic pain. Open surgery is common for patients requiring radical or partial nephrectomy and is associated with a high incidence of severe immediate postoperative pain and chronic pain in the months following surgery. Effective control of postoperative pain is a major challenge to treating surgeon and attending anaesthesiologist. Postoperative analgesia following renal surgeries is essential to allow effective coughing, early mobilization, and to reduce postoperative pulmonary complications.

Epidural analgesia (EA) significantly improves postoperative analgesia, reduce postoperative morphine consumption, decrease the area of wound hyperalgesia, and accelerate patient rehabilitation.[1] Epidural analgesia is a time tested method for management of postoperative pain, but as it is invasive, technique acceptability could be less. Epidural catheters may be placed incorrect, or become dislodged during the course of treatment. Transforaminal migration of the catheter tip and asymmetric spread have been described during epidural analgesia.[2] Secondary migration of the catheter after successful initial placement can occur.[3] During normal patient movement, epidural catheters may be displaced by centimetres. Local anaesthetic agents in combination with opioids are frequently used for this purpose, but development of hypotension is a major concern, also other side effects such as hemodynamic instability, urine retention, motor/sensory disturbances. Intermittent bolus epidural drug administration carries a risk of high plasma concentration soon after administration and later the drug levels gradually drop to subtherapeutic levels leading to development of pain. Hence safest mode of epidural administration will be giving the drug as infusion. However the need of an infusion pump for this purpose limits its regular use owning to high cost. Also , continuous epidural infusion has some disadvantages, such as increased local anaesthetic consumption and a limited area of anaesthetic distribution.[4]

Transdermal drug delivery systems (TDDS) are dosage forms involving drug transport to viable epidermal/ dermal tissues of the skin for local therapeutic effect while a very major fraction of drug is transported into the systemic blood circulation.[5] Several important advantages of transdermal drug delivery are limitation of hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug.[6] Buprenorphine transdermal system (BTDS,5-20 mcg/hr every 7 days) is the first 7 day sustained opioid formulation. Transdermal buprenorphine patches are now increasingly used for management of postoperative pain. There are 5 patch strengths available now: 5,7.5,10,15, and 20 ug/hr. Potential advantage for use of the buprenorphine patch includes the convenience of the dosing interval, which allows for once weekly patch application versus oral opioids that may

need to be taken multiple times per day. Additionally, the use of a transdermal patch may be beneficial in patients who are unable to swallow or in patients with nausea or vomiting.[5] Applying the patch on for 1 week allows patients to maintain more consistent blood levels versus using oral medications, which result in more frequent peaks and troughs.

Studies about the use of transdermal buprenorphine patches in postoperative analgesia are few and some have contradictory results which could be because the trials were performed in different type of surgeries, which can influence the degree of pain that is perceived. Epidural analgesia is the gold standard but since it is invasive and has risk of side effects like hypotension, infection, motor blockade etc. So we conducted a study to evaluate the efficacy of transdermal buprenorphine (10 mg) patch with continuous epidural infusion for postoperative analgesia following renal surgeries.

METHODS

The present study was a single centre , randomized control trial for one year. The study was approved by institute Ethics Committee and registered in the Clinical Trials Registery-India (CTRI/2020/10/028481) and written informed consent was taken. The study was conducted to compare and evaluate the postoperative analgesic efficacy of transdermal buprenorphine patch (10 mg patch) with continuous epidural infusion for postoperative analgesia in renal surgery patients. Total sample size was 40.Patients were randomized into two equal groups of 20 each. Inclusion criteria included ASA Status I and II, age group 20-60 yrs, weight 40-70 kg and height between 5 ft to 6 ft.

Those who were allergic to buprenorphine or have a history of allergy to opoids or patients having skin allergy were excluded from this study. Patients were allocated into 2 equal groups of 20 each using computer generated random sequence of numbers. In GROUP I patients, a transdermal buprenorphine patch 10 mg was applied 20-24 hr before the surgery i.e at the time of pre anaesthetic check up. In GROUP II patients, an epidural catheter was placed at the day of surgery under local anaesthesia at L2-L3 level.

All patients received general anaesthesia following standardized anaesthesia protocol. Patients were induced with propofol 1-2 mg/kg, muscle relaxation provided by atracurium plus inj fentanyl was given to dose of 2 mcg/kg at induction and 1 mcg/kg every hour and anaesthesia was maintained with oxygen, nitrous oxide, and isoflurane with mechanical ventilation. At the end of surgery, patients were extubated on table following reversal of neuromuscular blockade with neostigmine and glycopyrrolate. Epidural infusion with 0.1% bupivacaine plus fentanyl 2 mcg/ml at rate of 6ml/hr was started 15-20 mins before extubation. Efficacy of pain was checked using Numeric Rating Scale , with 0 being no pain and 10 being worst pain and two groups were compared at 30 mins, then 1hr post surgery for 6hrs then 2 hourly till 24 hrs. Numeric rating score of 4 or more was given rescue analgesia in form of fentanyl 1 mcg/kg/hr to max of 2 mcg/kg/hr. Rescue analgesic consumption if required was documented. The incidence of adverse effects like sedation, nausea, vomiting, itching, desaturation, respiratory depression and headache were observed in both groups. In absence of adverse effects, buprenorphine patches were kept in place for 7 days to provide postoperative analgesia.

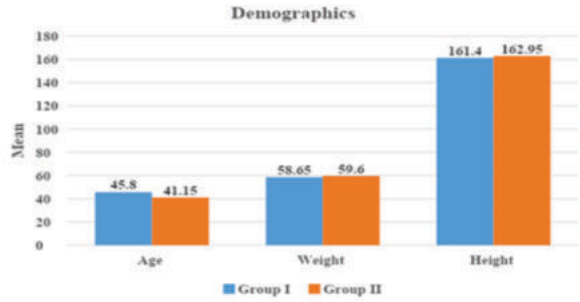
Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. Results on continuous measurements were presented on Mean ± SD (Min-Max) & categorical as Frequency (Percentage). Normality of the data was assessed using Shapiro Wilk test/ Kolmogorov-Smirnov test. Inferential statistics like Chi-square test/Fischer Exact test and Independent t test was applied. The significance of level adopted was 5%.

The primary outcome was to compare postoperative analgesia in form of Numeric Rating Scale (NRS) of transdermal buprenorphine patch (10mg) with continuous epidural infusion for postoperative analgesia in renal surgeries (Bupivacaine 0.1% + fentanyl 2ug/ml).

RESULTS

The present study was conducted in randomized control manner in ASA I and ASA II patients. Patients were allocated into 2 equal groups of 20 each using computer generated random sequence of numbers.

The baseline demographic variables were similar in both the groups. {Table 1}{fig 1}



{Fig 1}

Table No.1: Demographics

	Group I (Mean±SD)	Group II (Mean±SD)	P value
Age (Year)	45.80 ± 12.67	41.15 ± 10.98	0.222
Weight (Kg)	58.65±4.46	59.60±4.56	0.510
Height (Cm)	161.40±4.95	162.95±4.83	0.323

Mean numeric rating scale was significantly higher in Group I as compared to Group II at all the time intervals. {Table 2}

Table No.2: Numeric Rating Scale (NRS)

NRS	Group I (Mean±SD)	Group II (Mean±SD)	P value
30 min	6.25± 0.44	3.75± 0.44	0.001*
01 hour	5.95± 0.22	3.55± 0.51	0.001*
02 hour	5.50± 0.51	3.00± 0.00	0.001*
03 hour	5.30± 0.47	3.00± 0.00	0.001*
04 hour	5.10± 0.31	3.00± 0.00	0.001*
05 hour	5.00± 0.00	2.95± 0.22	0.001*
06 hour	4.90± 0.31	2.80± 0.41	0.001*
08 hour	4.35± 0.49	2.65± 0.49	0.001*
10 hour	4.10± 0.31	2.30± 0.47	0.001*
12 hour	4.00± 0.00	2.05± 0.22	0.001*
14 hour	4.00± 0.00	2.00± 0.00	0.001*
16 hour	3.50± 0.51	2.00± 0.00	0.001*
18 hour	3.05± 0.22	2.00± 0.00	0.001*
20 hour	3.00± 0.00	1.75± 0.44	0.001*
22 hour	3.00± 0.00	1.50± 0.51	0.001*
24 hour	3.00± 0.00	1.45± 0.51	0.001*

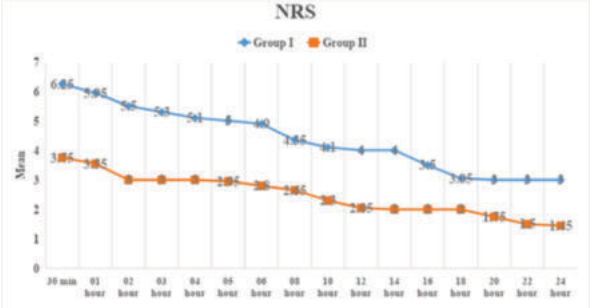


Table No.3: Rescue Analgesic: Fentanyl (ug)

Rescue Analgesic: Fentanyl in ug	Group I (Mean±SD)	Group II (Mean±SD)	P value
30 min	59.50±11.58	60.28 ±13.88	0.852
01 hour	0.00±0.00	0.00±0.00	-
02 hour	59.50±11.58	0.00±0.00	0.001*
03 hour	55.63±10.50	0.00±0.00	0.001*
04 hour	60.00±11.67	0.00±0.00	0.001*
05 hour	55.79±10.49	0.00±0.00	0.001*
06 hour	58.24±11.03	0.00±0.00	0.001*
08 hour	60.00±11.86	0.00±0.00	0.001*
10 hour	60.00±11.67	0.00±0.00	0.001*
12 hour	59.50±11.58	0.00±0.00	0.001*
14 hour	0.00±0.00	0.00±0.00	-
16 hour	0.00±0.00	0.00±0.00	-
18 hour	0.00±0.00	0.00±0.00	-
20 hour	0.00±0.00	0.00±0.00	-
22 hour	0.00±0.00	0.00±0.00	-
24 hour	0.00±0.00	0.00±0.00	-

In Group I, Mean rescue analgesic was 59.50±11.58, 0.00±0.00, 59.50±11.58, 55.63±10.50, 60.00±11.67, 55.79±10.49, 58.24±11.03, 60.00±11.86, 60.00±11.67 & 59.50±11.58 at 30 mins, 01 hour, 02 hour, 03 hour, 04 hour, 05 hour, 06 hour, 08 hour, 10 hour and 12 hours respectively. No rescue analgesic was given after 12 hours as shown in table 3.

In Group II, Mean rescue analgesic given at 30 mins was 60.28±13.88. However no rescue analgesics were given in Group II after 30 mins as shown in table 3.

Table no. 3

DISCUSSION

Postoperative pain is a major cause of morbidity and mortality in patients. The physician faces a difficult task in providing adequate pain management because there are numerous negative psychological and physiological repercussions linked with pain. Pain can obstruct normal recovery and lengthen hospital stays, as well as lead to patient dissatisfaction, a negative view of hospital performance, and increased health-care utilisation costs.

Traditional approaches like epidural analgesia and opioid based i.v. patient controlled analgesia (PCA), though associated with superior pain control, fail to translate into overall improved recovery or reduced morbidity when compared with pain management strategies used within an enhanced recovery after surgery pathway due to practical, equipment and management issues. Following major surgeries, epidural analgesia is probably the gold standard to provide optimal results, but it has inherent problems of being invasive and may lead to side effects like hypotension etc. The alternative approach of transdermal administration, relatively newer one in pain management protocols can also be used. Transdermal patches offer the advantage of sustained drug delivery, bioavailability, and avoidance of first-pass metabolism which reduces systemic effects. They have a one-time application so reduce workload on health care workers, and also prevent waxing waning of analgesia due to diminishing blood levels.

Most of the previous studies that have been done on transdermal patches, or comparison of patch to other intravenous opoid analgesics. Very few studies have been done on comparison of transdermal patch with epidural. Higher scores on mean NRS were recorded for group I as compared to group II which showed that transdermal buprenorphine didn't provide adequate analgesia as compared to epidural infusion. On statistical analysis, significant difference was observed between the two groups at all time periods ($p<0.05$) which showed that continuous epidural infusion was much better than buprenorphine patch throughout. The result of our study was in accordance with the study done by **Rajan et al** in which they had studied two groups in major abdominal surgeries ,one group received a transdermal buprenorphine 10 mg patch, ~20–24h before surgery, in other group an epidural catheter was placed at the start of the surgery and buprenorphine 150 μg in 10 ml saline was given epidurally. Numerical rating score was significantly higher in transdermal group ranging from (3-5) at 0 to 24hrs as compared with group E where it was (0-1) in the same time period, ($P<0.05$).[7]

Nidhi et al also conducted a study to compare postoperative analgesia with transdermal fentanyl patch and epidural fentanyl in lower limb orthopaedic surgeries. One group received transdermal fentanyl patch 25mcg/hr which was applied 14 hours before the starting of surgery, while patients group B received Epidural fentanyl (diluted with normal saline) before the surgery. Patients in the epidural fentanyl group had mean VAS scores ranging from (3-5) compared to transdermal fentanyl group with mean VAS scores (3-6) from 0-24 hrs (p less than 0.05), which was similar to our results.[8]

In a study by **Rajan et al** , the need for rescue analgesia was significantly higher in group transdermal buprenorphine (T) as compared with group epidural (E) group. ($P=0.001$). The intraoperative fentanyl consumption was significantly higher in group T (200±22.4 vs. 141.8±28.9, $P<0.001$). This correlated with our study in which transdermal patch group required rescue analgesia ranging from 30 mins till 12 hrs whereas in other group was given only till 30 mins.[7]

In our study, transdermal buprenorphine patch did't provide adequate analgesia in the initial 24 hrs post operatively. This could be because adequate plasma levels of buprenorphine were not attained by that time period. However, earlier patch placement in the absence of pain stimulus has many implications, as it might expose the patient to greater risk of excessive sedation, respiratory depression, nausea, and vomiting. Therefore, if the patches are to be applied 48-72 hrs before surgery, the patient should be under careful monitoring for early detection of any side effects.

The strength of patch and time of application before surgery were found to be the important factors affecting the efficacy of the patch.

The reported results are derived from few clinical trials, so more studies are necessary to confirm the safety and efficacy of buprenorphine compared to other analgesics or different buprenorphine dosages for postoperative pain. NRS used for pain assessment in this study is thought to be a subjective method. The definite conclusion regarding the efficacy of drug absorption following transdermal administration can be made by regular estimation of plasma concentration of buprenorphine in postoperative hours. Further more studies with larger sample size are required to validate the results.

CONCLUSION

Though continuous epidural infusion is more effective for postoperative analgesia, transdermal buprenorphine patch can be used particularly in the setting where pain may last for several days. It can reduce postoperative rescue analgesic consumption over 48 hours and maintain haemodynamic stability without serious complications like respiratory depression, sedation or postoperative nausea and vomiting.

However there is need for exploring further observation in other surgeries also as being non invasive it can be used as in cases where contraindication to placement of epidural catheter exists.

Conflict of Interests: Nil.

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