

Research Paper

Transdermal Buprenorphine versus Intramuscular Diclofenac for Postoperative Analgesia following Upper Abdominal Surgery under General Anesthesia: A Randomized Controlled Trial

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Abstract

Aim: To compare the post-operative analgesic effect of buprenorphine 20 µg/h patch with diclofenac 75 mg intramuscular injection following upper abdominal surgery under general anesthesia (GA). **Materials and Methods:** An open-label, randomized, controlled trial (CTRI/2018/03/012694) was conducted with adult subjects of either sex, undergoing planned major upper abdominal surgery under GA. Preoperative medication regimen and anesthesia protocol were uniform for all patients. Buprenorphine patch was applied to a hairless area of the chest or upper arm 12 h before surgery. Diclofenac 75 mg was injected into the deltoid muscle just after extubation. Postoperatively, vital signs were monitored along with Ramsay sedation scale (RSS) score. Postoperative analgesia was assessed using visual analog scale (VAS) scoring, at 4-h interval for the first 12 h and then 12-hourly for the next 2 days. Tramadol 2 mg/kg intravenous was permitted as a rescue analgesic. **Results:** Each arm had 35 patients without dropouts. The groups remained comparable in VAS pain score at all time points. However, with buprenorphine, although VAS score declined over time, the reduction attained statistical significance in comparison to the baseline (4 h) VAS score only at 72 h. In contrast, with diclofenac, VAS score achieved statistically significant reduction from 8 h onward and this was maintained throughout. In the buprenorphine arm, 21 patients (60.00%) required rescue analgesia in contrast to 10 (28.57%) on diclofenac ($P = 0.016$). Vital parameters and RSS remained essentially unchanged in both groups. **Conclusion:** Although the primary outcome measure was comparable between the groups, the pattern of rescue analgesia use suggests that postoperative analgesia experience with buprenorphine patch was less satisfactory than diclofenac injection in this study.

Keywords: Buprenorphine, diclofenac, postoperative analgesia, transdermal patch

INTRODUCTION

Postoperative pain is a major concern for patients undergoing abdominal surgery. Pain can be associated with adverse physiological and psychological effects hampering the normal recovery process.^[1] These include increased risk of deep vein thrombosis and pulmonary embolism, delayed wound healing, and demoralization.^[1] Preemptive analgesia, initiated before the surgical procedure, can theoretically reduce pain sensitization, but multiple clinical studies have failed to demonstrate convincing clinical benefit.^[2] It is now emerging that nociception after surgery is maintained by neuronal sensitization and afferent barrage from sensitized nociceptors all through the postoperative period, which is a mechanism distinct from other types of injury.^[3] Therefore, adequate

postoperative pain relief must be an integral part of the administration of anesthesia.^[4] Various drugs and techniques have been used to relieve postoperative pain, with varying degree of success.^[3] Each technique has its pros and cons.

Buprenorphine,^[5,6] 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. This

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How to cite this article: Basunia SR, Laha B, Hazra A. Transdermal buprenorphine versus intramuscular diclofenac for postoperative analgesia following upper abdominal surgery under general anesthesia: A randomized controlled trial. *J Pharmacol Pharmacother* 2019;10:57-62.

Received: 21-01-2019 **Revised:** 03-03-2019 **Accepted:** 24-06-2019

probably accounts for its longer duration of action compared to morphine, the unpredictability of its reversal by opioid antagonists, and its low level of manifest physical dependence. The lack of delta receptor agonist activity may be responsible for the observation that buprenorphine is less likely to induce tolerance on chronic use. The physical dependence potential is less compared to morphine.^[7]

Buprenorphine is used clinically for the treatment of moderate-to-severe pain, including perioperative analgesia.^[7,8] A transdermal patch formulation of buprenorphine has recently been introduced in the Indian market. Although expensive, this mode of delivery has several potential benefits over oral and parenteral administration.^[9] These include noninvasive dosing, better absorption, lack of first-pass metabolism, and steady plasma concentration. The buprenorphine patch releases the analgesic steadily over 7 days and has been successfully used to treat a variety of chronic pain conditions.^[9,10] However, there is limited clinical experience of its utility in postoperative pain.^[11,12]

We planned a randomized controlled trial to compare the effectiveness and safety of transdermal buprenorphine with the widely used parenteral analgesic, diclofenac, for postoperative analgesia in the setting of major upper abdominal surgery under general anesthesia (GA).

MATERIALS AND METHODS

The study was a prospective, parallel group, open label, randomized, controlled trial, over 1 year, in a district level teaching hospital. The study protocol conforms to the Declaration of Helsinki and was duly approved by the Institutional Ethics Committee (IEC) for clinical research (Approval letter No. IEC/2017/1 dated November 09, 2017). The trial has been registered with the Clinical Trial Registry-India (CTRI/2018/03/012694). This was an investigator-initiated study conducted with institutional resources. There was no commercial sponsor.

Study participants were patients of either sex, aged 18–65 years, and of the American Society of Anesthesiologists Grade 1 or 2, posted for planned major upper abdominal surgery under GA. Pregnant or breastfeeding women, patients allergic to study drugs, or those with the critical compromise of cardiopulmonary, hepatic, renal, or neurological function were excluded from the study. Sampling was purposive. During preanesthetic check-up, eligible patients were informed about the study. Those who provided written informed consent were familiarized with the application of the transdermal patch and use of the visual analog scale (VAS) for pain assessment.

Patients were allocated to two parallel study groups by simple, balanced randomization using a computer-generated random number list. Allocation concealment was achieved by the serially numbered opaque sealed envelope technique. Randomization and allocation concealment responsibility was taken by a pharmacologist not otherwise involved

in day-to-day study procedures. One group received buprenorphine patch (BUVALOR patch marketed by Modi Mundipharma Pvt., Ltd., New Delhi) releasing 20 µg/h. The patch was cited on a hairless area of the chest or upper arm, 12 h before the operation. The patch was removed on the 7th day if the patient stayed in the hospital, or asked to do so if discharged earlier. The other group received diclofenac sodium intramuscular (IM) injection, in aqueous solution, 75 mg in the deltoid region. The first dose was given just after extubation, and thereafter, the same dose of 75 mg was repeated every 12 h till the end of the observation period of 72 h. Subsequent dosing was titrated to response.

All patients were premedicated on the night before surgery with ranitidine 150 mg and alprazolam 0.25 mg orally. In the preoperative holding area, 18G cannula was inserted, and baseline hemodynamic parameters, namely heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were noted. At the time of surgery, patients received midazolam 1 mg by intravenous (IV) route, fentanyl 2 µg/kg IV, and ondansetron 4 mg IV. Anesthesia was induced with propofol 2 mg/kg IV and intubation was done with succinylcholine 1 mg/kg IV. Maintenance was by nitrous oxide with oxygen (60:40) and isoflurane. Muscle relaxation was maintained with vecuronium 0.08 mg/kg IV. Paracetamol 1000 mg by IV infusion was given during the maintenance phase. At the end of the surgery, patients were extubated after reversing neuromuscular blockade with neostigmine (0.05 mg/kg) and glycopyrrolate (0.2 mg for each 1 mg neostigmine) IV. After adequate recovery (Aldrete score >8), all patients were extubated and shifted to the postanesthesia care unit for observation. Each patient was monitored in the postoperative period for hemodynamic parameters, namely HR, SBP, and DBP and oxygen saturation by pulse oximetry.

The primary outcome measure was postoperative pain assessed by VAS scoring at 4-h intervals for the first 12 h and then 12 hourly till the end of 72 h. For VAS scoring, a 10 cm vertical line was used, marked out in millimeters. The patient was asked to indicate a spot on the line corresponding to his or her perceived intensity of pain at the moment, assuming that the lowest point on the line (0 mm) represented zero pain while the highest point (100 mm) represented the worst pain imaginable. The distance from the origin of the line to the marked spot was then recorded. A fresh VAS scoring line was used at each assessment to ensure that the patient's opinion was not influenced by the position of an earlier mark. Rescue analgesic in the form of tramadol injection 2 mg/kg IV (to maximum 100 mg) was administered on demand or when VAS reached 4 cm or more. Total rescue analgesia requirement was recorded.

Drowsiness was assessed using the Ramsay sedation scale (RSS) score at the same time points as VAS scoring. The number of episodes of nausea-vomiting (despite postoperative ondansetron 4 mg 8-hourly for 48 h) was noted. Changes in vital parameters and other potential treatment-emergent adverse events were recorded.

The target sample size was 35 evaluable patients in each group. This was calculated to detect a difference of 30 in VAS pain score between groups at 24-h postoperative with 80% power and 0.05 probability of type 1 error, assuming a standard deviation of 45 for VAS score and two-sided testing. Sample size calculation was done using nMaster 2.0 (Vellore: Department of Biostatistics, Christian Medical College; 2011) software. Allowing for a 10% dropout rate, the recruitment target was set at 39 patients per group.

Data have been summarized by routine descriptive statistics, namely mean and standard deviation for numerical variables that are normally distributed, median, and interquartile range (IQR) for skewed numerical variables and counts and percentages for categorical variables. Numerical variables were compared between groups by Student’s independent samples *t*-test if normally distributed, or by Mann–Whitney U-test, if otherwise. Fisher’s exact test was employed for intergroup comparison of categorical variables. Changes over time in numerical variables were assessed for statistical significance by repeated measures analysis of variance (ANOVA) or Friedman’s ANOVA, as appropriate, followed by *post hoc* testing. All analyses were two-tailed, and the statistical significance level was set at $P < 0.05$ for all. Analyses were performed using Statistica 6.0 (Tulsa, Oklahoma: StatSoftInc., 2001) and GraphPad Prism (version 5 San Diego, California: GraphPad Software Inc.,2007) software.

RESULTS

Eighty patients were screened, of whom ten were not included because of violation of the exclusion criteria or lack of confidence in handling pain scoring. Seventy were randomized to study treatments and since none were lost to follow-up, the recruitment was closed after 70 patients. The patient disposal has been depicted in the Consolidated Standards for Reporting Trials (CONSORT) style flow diagram in Figure 1.

The groups were evenly matched at baseline with respect to age and other baseline clinical characteristics, as depicted in Table 1.

Table 2 presents the serial changes in VAS score for pain over time in the two study groups. The groups remained comparable at all observation time points. In the buprenorphine group, although the VAS score declined over time, the reduction attained statistical significance in comparison to the baseline (4 h) VAS score only at 72 h. In contrast, in the diclofenac group, VAS score achieved a statistically significant reduction in comparison to baseline from 8 h onwards, and this was maintained until the end of the observation period.

There were no significant changes over time in vital parameters in either group – *P* value from repeated measures ANOVA being 0.106, 0.528, and 0.108 for HR, SBP, and DBP, respectively, in buprenorphine patch users and 0.441, 0.174, and 0.349 in diclofenac injection recipients.

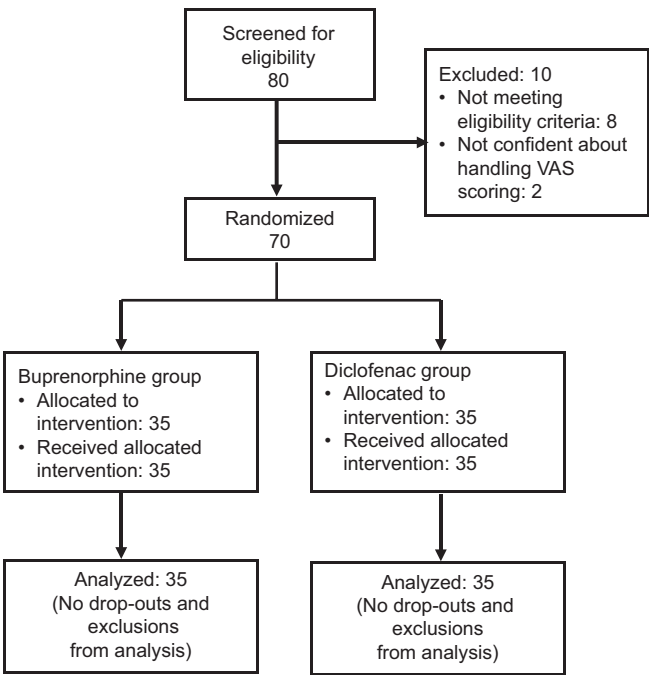


Figure 1: Flowchart showing patient disposal in the study

Table 1: Comparison of demographic and baseline characteristics between the study groups (n=35)			
Parameters	Buprenorphine group, n (%)	Diclofenac group, n (%)	P
Age (years)			
Range	25-60	18-65	0.689
Mean±SD	42.2±9.63	43.3±12.75	
Gender			
Male	18 (51.43)	16 (45.71)	0.811
Female	17 (48.57)	19 (54.29)	
Weight (kg)			
Range	28-80	40-80	0.427
Mean±SD	56.1±11.71	58.1±9.76	
ASA grade			
I	9 (25.71)	7 (20.00)	0.777
II	26 (74.29)	28 (80.00)	

P value in the last column is from Student’s independent samples *t*-test for the numerical variables and Fisher’s exact test for gender distribution and ASA grade. ASA=American Society of Anesthesiologists, SD=Standard deviation, IQR=Interquartile range

In the buprenorphine group, RSS score changed over time from 3.00 (2.00–3.00) (median [IQR]) at 4 h to 2.00 (2.00–2.00) at 72 h. This was not significant statistically. Similarly, in the diclofenac group, there was nonsignificant change in RSS from 3.00 (2.00–3.00) at 4 h to 2.00 (2.00–3.00) at 72 h. The Ramsay Sedation Scale has 6 score levels, with score 2 indicating that the subject is cooperative, orientated and tranquil; score 3 indicates that the subject is drowsier but responds to verbal commands. Therefore, effectively, neither study drug produced major sedation in the doses used.

Table 2: Changes in visual analog scale scoring of pain over time

Parameters	Buprenorphine group (n=35)	Diclofenac group (n=35)	P
VAS at 4 h			
Range	1.0-5.0	3.0-4.0	0.787
Mean±SD	3.0±0.91	3.1±0.32	
Median (IQR)	3.0 (3.0-3.0)	3.0 (3.0-3.0)	
VAS at 8 h			0.103
Range	1.0-5.0	2.0-4.0	
Mean±SD	3.1±0.76	2.9±0.53	
Median (IQR)	3.0 (3.0-4.0)	3.0 (3.0-3.0)	
VAS at 12 h			0.118
Range	1.0-5.0	2.0-3.0	
Mean±SD	2.8±0.71	2.6±0.50	
Median (IQR)	3.0 (3.0-3.0)	3.0 (2.0-3.0)*	
VAS at 24 h			0.711
Range	1.0-4.0	2.0-3.0	
Mean±SD	2.6±0.81	2.5±0.51	
Median (IQR)	3.0 (2.0-3.0)	3.0 (2.0-3.0)**	
VAS at 36 h			0.250
Range	1.0- 4.0	2.0- 4.0	
Mean±SD	2.4±0.78	2.6±0.61	
Median (IQR)	2.0 (2.0-3.0)	3.0 (2.0-3.0)**	
VAS at 48 h			0.934
Range	1.0-4.0	2.0-3.0	
Mean±SD	2.2±0.69	2.4±0.49	
Median (IQR)	2.0 (2.0-3.0)	2.0 (2.0-3.0)***	
VAS at 60 h			0.577
Range	1.0- 3.0	2.0-4.0	
Mean±SD	2.2±0.60	2.4±0.60	
Median (IQR)	2.0 (2.0-3.0)	2.0 (2.0-3.0)***	
VAS at 72 h			0.438
Range	1.0-3.0	1.0-3.0	
Mean±SD	2.2±0.55	2.3±0.59	
Median (IQR)	2.0 (2.0-3.0)**	2.0 (2.0-3.0)***	
P value for within group comparison	<0.001	<0.001	

P value in the last column is from Man-Whiney U-test; P value for within group comparison is from Friedman's ANOVA. *, **, ***P<0.05, 0.01, 0.001 in comparison to baseline. SD=Standard deviation, IQR=Interquartile range, VAS=Visual analog scale, ANOVA=Analysis of variance

In the buprenorphine group, 21 patients (60.00%) required rescue analgesia within the 72 h observation period, in contrast to 10 (28.57%) in the diclofenac group. This difference was statistically significant ($P = 0.016$). Further 10 of the 21 patients (47.62%) in the former group required rescue twice, in contrast to 2 of the 10 (20%) – this was, however, not a significant difference ($P = 0.693$). Figure 2 depicts comparison of rescue analgesia use in the two study groups.

No serious adverse effects were encountered in our study, and there was no prolongation of hospitalization on this count. Apart from sedation and mild pain during diclofenac injection, other adverse events, attributable to study drugs, were not encountered. There were no local skin irritation problems with the transdermal patch formulation.

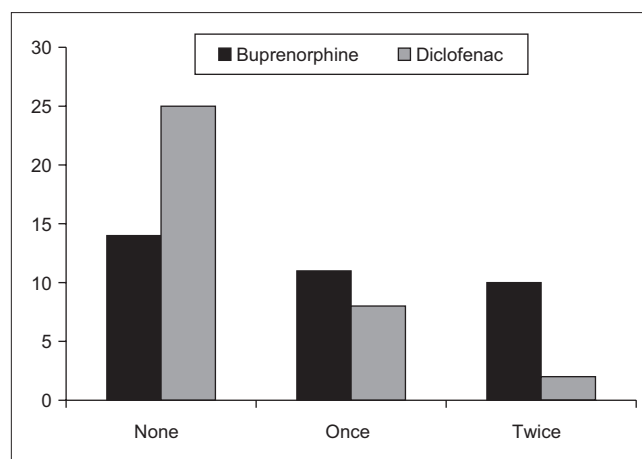


Figure 2: Comparison of rescue analgesia requirement (number of times used) between the groups. The difference is statistically significant ($P = 0.011$ by Chi-square test)

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. Injectable formulations of the drug require skilled administration that may be inconvenient and provide a bolus effect that may be poorly tolerated, particularly in the elderly.^[13] Its high binding affinity and slow receptor dissociation are properties that could potentially provide long-lasting action from a transdermal patch formulation that is easily applied to postoperative patients. Such a formulation allows the noninvasive method of rate-controlled drug release to ensure steady and predictable plasma buprenorphine levels over a prolonged period. In fact, the buprenorphine transdermal patch was developed with the intention to extend the utility of the drug from cancer pain, the traditional indication for injectable opioids, to other types of pain.^[14] It was first launched in Switzerland and Germany in 2001 and is now marketed worldwide. Clinical experience suggests that this mode of use is acceptable to patients with the potential adverse reactions (nausea, vomiting, drowsiness, dizziness, constipation, and headache) being tolerable.^[15] It is also safe to use in the elderly and patients with renal impairment.^[16]

Apart from cancer pain, transdermal buprenorphine has been used successfully to treat osteoarthritis, chronic musculoskeletal pain^[17,18] and chronic neuropathic pain.^[19,20] The efficacy and safety aspect of its use has received favorable review,^[21] though it is noteworthy that response rates have been well short of 100% in most indications.

Though widely used, diclofenac injection is not an ideal choice for postoperative pain relief because of its potential complications, particularly in elderly and renally compromised patients. It is also preferably avoided in stomach and duodenal surgery. 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. The use of transdermal buprenorphine for perioperative or postoperative analgesia is being explored relatively recently. A recent study^[22] has found it to compare well with oral tramadol/paracetamol for postoperative pain relief following spinal surgery. In an Indian study,^[23] 50 patients undergoing surgery for hip fracture under spinal anesthesia were given either transdermal buprenorphine 10 µg/h patch applied a day before the surgery or oral tramadol 50 mg three times a day. Diclofenac and paracetamol tablets were allowed for rescue analgesia. The authors reported that transdermal buprenorphine was more effective in reducing postoperative pain after 24 h, with fewer adverse effects compared to oral tramadol. In another Indian study,^[11] 60 patients undergoing major abdominal surgery under GA were randomized to receive transdermal buprenorphine 10 µg/h or transdermal fentanyl 25 µg/h, 6 h before surgery, and followed up for 72 h. Although both drugs were effective and safe in controlling postoperative pain, fentanyl was better in terms of requirement of rescue analgesic.

In this study, which extended to 72 h observation postoperatively, we also found both transdermal buprenorphine and IM diclofenac to be comparable in reducing the VAS pain scores. However, in terms of rescue analgesic requirement, there was a statistically significant advantage of diclofenac over transdermal buprenorphine. This goes against the tenet of the other studies for postoperative pain relief, as cited above, where the experience with buprenorphine was not inferior to the comparator. It is noteworthy that we used a 20 µg/h patch in contrast to the two Indian studies^[11,23] that used a lower dose, that is 10 µg/h patch. The earlier studies have not reported severe or serious adverse reactions with buprenorphine patch and the prescribing literature of the 20 µg/h patch also indicates that it is likely to be safe.

We do not have a convincing explanation of why transdermal buprenorphine did not perform as well as expected, as indicated by the slower rate of decline in VAS score for pain and extent of rescue analgesia requirement. One possible reason is that postoperative pain is more inflammatory in character and therefore has responded better to the anti-inflammatory analgesic in this case rather than the opioid buprenorphine. Another reason could be that the zero-order drug release profile of the patch does not allow sharp peak of plasma concentration that would suppress peaks of postoperative pain intensity.

This study has its share of limitations. The nonblinded nature can introduce bias in the evaluation of pain through VAS scoring. However, double blinding would have required a dummy patch and a sham injection, both of which were not feasible in our setting. Rescue analgesia was offered on demand rather than strictly in accordance with the VAS score.

CONCLUSION

We can say that although the buprenorphine patch provided comparable analgesia to diclofenac injection when VAS

scores were compared at different time points, the overall postoperative analgesia experience with buprenorphine was less satisfactory. Buprenorphine arm required more rescue analgesia, and it took longer for the VAS score to decrease significantly from the baseline. Therefore, despite its noninvasive nature and excellent tolerability, in view of the much higher cost of the patch, we cannot recommend it as a regular alternative to diclofenac injection for postoperative analgesia following upper abdominal surgery.

Financial support and sponsorship

The study was done using departmental funds. Study drugs were supplied from the hospital.

Conflicts of interest

There are no conflicts of interest.

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