Original research article

Postoperative pain assessment using transdermal buprenorphine versus intramuscular diclofenac for analgesia: a randomized comparative trial

Dr. Rakesh Kumar[1], Dr. Narendra Kumar[2], Dr.Chhabindra Kumar[3], Dr.Pradip Kumar Gyani[4]

[1]Senior Resident, Department of Anaesthesiology, Government medical College and Hospital, Bettiah, Bihar, India.

[2]Associate Professor and HOD, Department of Anaesthesiology, Government medical College and Hospital, Bettiah, Bihar, India.

[3]Assistant Professor, Department of Anaesthesiology, Government medical College and Hospital, Bettiah, Bihar, India.

[4]Assistant Professor, Department of Anaesthesiology, Government medical College and Hospital, Bettiah, Bihar, India.

Corresponding Author: Dr.Narendra Kumar

Abstract

Aim: 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).

Material and methods: This was prospective, controlled clinical trial done in the Department of Anaesthesiology Government medical College and Hospital, Bettiah, Bihar, India for one year. Patients were allocated to two parallel study groups by simple, balanced randomization using a computer-generated random number list. One group received buprenorphine patch releasing 20µg/h. The other group received diclofenac sodium intramuscular (IM) injection, in aqueous solution, 75 mg in the deltoid region. 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 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 50 evaluable patients in each group.

Results: 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. In the buprenorphine group, 31 patients (62%) required rescue analgesia within the 72 h observation period, in contrast to 12 (24%) in the diclofenac group. This difference was statistically significant (P = 0.012).

Conclusion: we concluded that 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

The International Association for the Study of Pain (IASP) has defined pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage'. Effective pain management facilitates easy recovery from

injury or surgery and aids rapid recovery of functions. Surgery results in damage to local tissue with consequent release of prostaglandins, histamine, serotonin, bradykinin, 5-hydroxytryptamine, substance P and leads to the generation of noxious stimuli that are transduced by nociceptors and transmission to the neuraxis by A-delta and C nerve fibers.[1] Patients undergoing surgeries experience acute postoperative pain and less than half report post-operative pain relief.[2] Postoperative pain management is a necessary component of patients undergoing major surgery as the postoperative pain hamper the normal recovery process, cause the extended length of hospital days, patient dissatisfaction, negative perception of hospital performance and increased healthcare utilization costs.[3] Transdermal drug delivery has several potential advantages over oral and parenteral administration as they are non-invasive, avoids gastrointestinal tract, lack the first-pass metabolism and maintain a sustained blood level of the drugs. Steady and continuous drug delivery avoids potential side-effects associated with repeated doses.[4] Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) exert anti-inflammatory and analgesic effects through the inhibition of prostaglandin synthesis, by blocking the activity of cyclo-oxygenase. The non-selective NSAID diclofenac transdermal patch is a newly introduced Transdermal Delivery System (TDS) that provides continuous and systemic release of diclofenac and is designed to remain at the site of application for 24 hours. Since the oral bioavailability of diclofenac is about 50%, to avoid first-pass metabolism, the transdermal route is an alternative choice.[1] Opioid analgesics are prescribed for moderate to severe pain, especially of visceral origin. The opioid patch is a drug reservoir separated from the skin by a membrane and the drug is released over a specific period of time. Buprenorphine is a semi-synthetic, centrally acting opium alkaloid derived from the baine and belongs to the 6,14-endo- ethano-tetrahydro-oripavine. It is a partial μ-receptor agonist and κ and δ receptor antagonist. After the removal of the patch, plasma concentration is reduced by ~50% in the first 12 hours.[4] 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).

Material and methods

This was prospective, controlled clinical trial done in the Department of Anaesthesiology, Government medical College and Hospital, Bettiah, Bihar, India for one year, after taking the approval of the protocol review committee and institutional ethics committee. 100 patients of either sex, aged 18–70 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.

Patients were allocated to two parallel study groups by simple, balanced randomization using a computer-generated random number list. One group received buprenorphine patch releasing 20μg/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 propanol 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 50 evaluable patients in each group.

Results

100 patients were included in this study and divided into two equally groups 50 in each groups. 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 0.112, 0.542, and 0.121 for HR, SBP, and DBP, respectively, in buprenorphine patch users and 0.434, 0.165, and 0.337 in diclofenac injection recipients In the buprenorphine group, RSS score changed over time from 3.2 (3.1–3.2) (median [IQR]) at 4 h to 2.2 (2.1–2.2) at 72 h. This was not significant statistically. Similarly, in the diclofenac group, there was non significant change in RSS from 3.2 (3.1–3.2) at 4 h to 2.2 (2.2–3.2) 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.

In the buprenorphine group, 31 patients (62%) required rescue analgesia within the 72 h observation period, in contrast to 12 (24%) in the diclofenac group. This difference was statistically significant (P = 0.012). Further 15 of the 31 patients(48.39%) in the former group required rescue twice, in contrast to 3 of the 12 (25%) – this was, however, not a significant difference (P = 0.654). 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.

Table 1: Comparison of demographic and baseline characteristics between the study groups (n=50)

Parameters	Buprenorphine group, n (%)	Diclofenac group, n (%)	P
Age (years)			
Range	24-60	18-59	0.621
Mean±SD	41.9±10.33	42.8±12.06	
Gender			
Male	27 (54)	21 (42)	0.756
Female	23 (46)	29 (58)	
Weight (kg)			
Range	27-81	38-79	0.463
Mean±SD	55.9±10.88	58.5±9.87	
ASG Grade			
I	12 (24)	9 (18)	0.723
II	38 (76)	41 (82)	

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

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

Parameters	Buprenorphine group (n=50)	Diclofenac group (n=50)	P
VAS at 4 h			
Range	1.0-6.0	2.0-4.0	0.736
Mean±SD	3.1±0.87	3.2±0.26	
Median (IQR)	3.2 (3.1-3.3)	3.2 (3.1-3.3)	
VAS at 8 h			0.121
Range	1.0-6.0	2.0-5.0	
Mean±SD	3.3±0.72	2.8±0.56	
Median (IQR)	3.1 (3.1-4.1)	3.1 (3.1-3.1)	
VAS at 12 h			
Range	1.0-6.0	2.0-4.0	0.136
Mean±SD	2.7±0.61	2.7±0.40	
Median (IQR)	3.2(3.1-3.1)	3.1 (2.1-3.1)*	
VAS at 24 h			
Range	1.0-5.0	2.0-4.0	0.638
Mean±SD	2.7±0.61	2.6±0.41	
Median (IQR)	3.1 (2.1-3.1)	3.1 (2.1-3.1)**	
VAS at 36 h			
Range	1.0- 6.0	2.0- 6.0	0.236
Mean±SD	2.6±0.72	2.8±0.66	
Median (IQR)	2.2 (2.2-3.2)	3.2 (2.2-3.2)**	
VAS at 48 h			
Range	1.0-5.0	2.0-5.0	0.875

Mean±SD	2.4±0.69	2.6±0.49	
Median (IQR)	2.1 (2.1-3.1)	2.1 (2.1-3.1)***	
VAS at 60 h			
Range	1.0- 4.0	2.0-5.0	0.532
Mean±SD	2.4±0.70	2.6±0.70	
Median (IQR)	2.2 (2.2-3.2)	2.2 (2.2-3.2)***	
VAS at 72 h			
Range	1.0-4.0	1.0-4.0	0.475
Mean±SD	2.4±0.52	2.5±0.63	
Median (IQR)	2.2 (2.2-3.2)**	2.2 (2.2-3.2)***	
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. *,**,*** .001 in comparison to baseline. SD=Standard deviation, IQR=Interquartile range, VAS=Visual analog scale, ANOVA=Analysis of variance

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.[5] 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.[6] 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.[7]It is also safe to use in the elderly and patients with renal impairment.[8]

Apart from cancer pain, transdermal buprenorphine has been used successfully to treat osteoarthritis, chronic musculoskeletal pain[9,10] and chronic neuropathic pain.[11,12]The efficacy and safety aspect of its use has received favorable review,[13] 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[14] has found it to compare well with oral tramadol/paracetamol for postoperative pain relief following spinal surgery. In an Indian study,[15] 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,[16] 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[15,16] 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.

Conclusion

We concluded that 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.

Reference

1. Kumar V, Gupta S, Verma R. Evaluation of the role of transdermal diclofenac patch (nupatch) in management of pain in postoperative patients. Int J Contemp Med Res. 2017;4(2): 493-496.
2. Chou R, Gordon D, de Leon-Casasola O, Rosenberg J, Bickler S, Brennan T et al. Guidelines on management of postoperative pain. J Pain. 2016;17(2): 131-157.
3. Kumar S, Kumar A, Chaudhary A K, Singh P K, Verma R, Chandra G, et al. Transdermal buprenorphine patches for postoperative pain control in abdominal surgery. J Clin Diagn Res. 2016;10(6): 5-6.
4. Das R, Mohanty S, Routray S S, Dash A, Sahoo D N. A comparative study between transdermal patches of Buprenorphine and Fentanyl for postoperative pain relief following orthopaedic surgery under regional anaesthesia. Sch J App Med Sci. 2017;5(4D): 1456-1462.
5. Mercadante S, Porzio G, Fulfaro F, Aielli F, Verna L, Ficorella C, et al. Switching from transdermal drugs: An observational "N of 1" study of fentanyl and buprenorphine. J Pain Symptom Manage 2007;34:532-8.
6. Kress HG. Clinical update on the pharmacology, efficacy and safety of transdermal buprenorphine. Eur J Pain 2009;13:219-30.
7. Likar R. Transdermal buprenorphine in the management of persistent pain – Safety aspects. Ther Clin Risk Manag 2006;2:115-25.
8. Al-Tawil N, Odar-Cederlöf I, Berggren AC, Johnson HE, Persson J. Pharmacokinetics of transdermal buprenorphine patch in the elderly. Eur J Clin Pharmacol 2013;69:143-9.
9. Conaghan PG, Serpell M, McSkimming P, Junor R, Dickerson S. Satisfaction, adherence and health-related quality of life with transdermal buprenorphine compared with oral opioid medications in the usual care of osteoarthritis pain. Patient 2016;9:359-71.
10. Yoon DH, Bin SI, Chan SK, Chung CK, In Y, Kim H, et al. Effectiveness and tolerability

of transdermal buprenorphine patches: A multicenter, prospective, open-label study in Asian patients with moderate to severe chronic musculoskeletal pain. BMC Musculoskelet Disord 2017;18:337.
11. Rodriguez-Lopez M. Transdermal buprenorphine in the treatment of neuropathic pain. Rev Soc Esp Dolor 2004;11:S11-21.
12. Penza P, Campanella A, Martini A, Melli G, Lombardi R, Camozzi F, et al. Short- and intermediate-term efficacy of buprenorphine TDS in chronic painful neuropathies. J Peripher Nerv Syst 2008;13:283-8.
13. Hans G, Robert D. Transdermal buprenorphine – A critical appraisal of its role in pain management. J Pain Res 2009;2:117-34.
14. Lee JH, Kim JH, Kim JH, Kim HS, Min WK, Park YS, et al. Efficacy and safety of transdermal buprenorphine versus oral tramadol/ Acetaminophen in patients with persistent postoperative pain after spinal surgery. Pain Res Manag 2017;2017:2071494.
15. Arshad Z, Prakash R, Gautam S, Kumar S. Comparison between transdermal buprenorphine and transdermal fentanyl for postoperative pain relief after major abdominal surgeries. J Clin Diagn Res 2015;9:UC01-4.
16. Desai SN, Badiger SV, Tokur SB, Naik PA. Safety and efficacy of transdermal buprenorphine versus oral tramadol for the treatment of post-operative pain following surgery for fracture neck of femur: A prospective, randomised clinical study. Indian J Anaesth 2017;61:225-9.

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