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EFFICACY OF TRANSDERMAL BUPRENORPHINE PATCH 10 MG ON POSTOPERATIVE PAIN CONTROL IN PATIENTS UNDERGOING SPINE SURGERY

Manjula B P — Professor , Dept of Anaesthesia Critical Care and Pain Medicine, JSS Medical College, Mysuru, Karnataka

Anand Mammen* — Junior Resident , Dept of Anaesthesia Critical Care and Pain Medicine, JSS Medical College, Mysuru, Karnataka *Corresponding Author

ABSTRACT Aim of this study is to evaluate the analgesic efficacy of transdermal buprenorphine patch 10 mg [10 µg/hr] in the management of acute post operative pain in patients undergoing elective spine surgery in terms of duration of post operative analgesia as the primary outcome. 60 patients aged 18- 55 yrs, posted for elective spine surgery, belonging to ASA class I and II were randomized into 2 equal groups, Group B and Group P. Transdermal Buprenorphine 10 mg patch was applied in Group B and Placebo patch was applied in Group P, 20 hrs before surgery. General anaesthesia was given to all patients. Post operatively Inj Diclofenac was administered as analgesic in both the groups. Inj.Tramadol was given as rescue analgesic whenever VAS >3. All patients were also monitored for drug related adverse effects and changes in hemodynamic status till post op day 5. Time to first post-operative rescue analgesic requirement was much delayed in Group B than in Group P [744.0 ± 8.64 min vs 61 ± 0.28 min, P<0.001]. We concluded that transdermal buprenorphine patch 10mg is effective in prolonging post-operative analgesia when applied 20 hrs before surgery.

KEYWORDS : transdermal patch ,buprenorphine ,spine surgery, post-operative analgesia

INTRODUCTION:

Experiencing pain has been the most common concern among surgical patients. It has been estimated that, more than 70 % of patients experience acute pain after surgery despite an increased focus on pain management and improved awareness[1]. Conventional spine surgeries often involve extensive dissection of subcutaneous tissue, bones and ligaments resulting in considerable degree of pain , especially for the initial few days. Inadequate management of pain in the acute postoperative period can lead to persistent post surgical pain.

Buprenorphine, a potent centrally acting opioid analgesic has been available for use in clinical practice in a variety of setting for over 30 years.[1] It is classified as a mixed opioid i.e. agonist – antagonist opioid compound due to its partial agonism at µ- opioid receptors. It is also an antagonist at κ-opioid receptors, an agonist at δ-opioid receptors and a partial agonist at ORL-1 (opioid receptor like 1) / nociceptin receptors[2].The analgesic activity of buprenorphine is mediated primarily via partial agonism at the µ-opioid receptor, although it is described to function as a pure µ receptor agonist for antinociceptive effects at clinically relevant doses[2]. But for µ receptor mediated respiratory depression, the partial agonist property is retained. Hence, at clinically relevant doses, buprenorphine exerts a ceiling effect for respiratory depression (due to its partial agonist activity) and not for analgesia.[2]

Buprenorphine was initially available in the injectable and sublingual formulations. Because of its low bioavailability, it is not useful by oral route[3]. The physical and chemical properties of buprenorphine like low molecular weight, high lipophilicity and high affinity for the µ opioid receptor makes it a well suited drug for transdermal delivery.[4] The availability of the transdermal preparation, which releases buprenorphine over a 7 day period, has led to resurgence in the use of the drug.

We evaluated the efficacy of transdermal buprenorphine patch 10 mg , releasing buprenorphine at a rate of 10mcg/hr over a period of 7 days, in the management of acute post surgical pain in patients undergoing elective spine surgery.

MATERIALS AND METHODS :

The study was conducted at JSS Medical College Hospital, Mysuru between November 2016 to July 2018, after obtaining approval from institutions ethical committee and written informed consent from the patients. Duration of post operative analgesia was taken as the primary objective. It was measured in terms of time to first dose of rescue analgesic. It was estimated that 16 subjects were required per group to detect 20 mins difference in this parameter with 80% power and 5% probability in Type I error, based on previous study. In our study 30 subjects were taken per group to compensate for any drop outs. Inclusion criteria: Patients with ASA grade I and II of either sex aged between 18 - 55 years. Exclusion criteria : Patients of ASA grade > II , age < 18 years and > 55 years, pregnant women or nursing mothers, patients on any other form of opioid therapy, opioid dependent and opioid sensitive patients , patients on other CNS depressants like benzodiazepines, current or recent treatment (within 2 weeks) with monoamine oxidase inhibitors, history of drug allergy or application site rashes were excluded. 60 patients who fulfilled the inclusion and exclusion criteria were randomized into 2 equal groups [Group B and Group P, n = 30 in each group] using a computer generated random number list and the allocation concealment was done by the serially numbered opaque sealed envelope technique.

Group B: Received transdermal buprenorphine patch 10 mg , 20 hrs before surgery.

Group P : Received placebo patch 20 hrs before surgery.During pre-anaesthetic evaluation , all patients were informed about the transdermal patch and were familiarized about visual analogue scale (VAS) based pain assessment. The transdermal patches were applied over hairless areas on the outer arm. The patches were covered with similar sizes of Dynaplast™ so that the external appearance of both the patches could not be differentiated by a third person. The anaesthesiologist who was involved with randomization of patients is the one who applies the patches and he is not involved further in the study. Thus the anaesthesiologist who recorded the study parameters and the patients were blinded for the study drug. All patients were pre-medicated on the night before surgery with tablet ranitidine 150 mg and alprazolam 0.5 mg orally. On the day of surgery, all the baseline parameters (heart rate [HR], blood pressure [BP], oxygen saturation [SpO2]) were recorded and intravenous (IV) line was established. Before induction, all the patients were premedicated with ondansetron 4mg IV, midazolam 1mg IV. After pre-oxygenation, anaesthesia was induced with IV propofol (2 mg/kg), lignocaine (1.5 mg/kg) and vecuronium (0.1 mg/kg) to facilitate intubation along with IV fentanyl (2 µg/kg). Anaesthesia was maintained with 60%N2O and 40%O2 along with isoflurane 1%–1.5% and vecuronium 0.01 mg /kg repeated every 20 mins . Ventilation was adjusted to maintain end-tidal CO2 between 35 and 40 mmHg.

Additional doses of fentanyl 25mcg IV, was administered as and when required until 30 min prior to skin closure to maintain mean arterial pressure (MAP) and HR around 20% of pre operative status. The number of additional doses of fentanyl 25 mcg IV administered in both groups was recorded. At the end of surgery, residual neuromuscular blockade was antagonised with IV neostigmine (0.05mg/kg) and glycopyrrolate (0.01 mg/kg). After adequate recovery all the patients were extubated and shifted to the post anaesthesia care unit (PACU) for observation. Intraoperative and postoperative hemodynamic parameters (HR , SBP , DBP , MAP) were compared between the two groups. Degree of analgesia was assessed by VAS score and sedation by RSS score up to post op day 5.

Postoperatively, Inj. Diclofenac 75 mg IM 12 hourly was administered as analgesic in both groups and injection tramadol 2 mg/kg (maximum 100 mg) IM or slow IV was administered whenever VAS >3, as rescue analgesic. The number of doses and total doses of Inj. Tramadol required in both the groups were recorded.

VAS is a simple, solid, sensitive, validated, and reproducible instrument that is useful for reassessing pain in the same patient on different occasions. VAS score of 1-3 suggest mild pain, 4-6 moderately severe pain and 7-10 intense pain.

Ramsay sedation score [RSS score] is used to asses level of sedation during intraoperative and post operative period. Ramsay sedation score , 1 = awake, 2 = drowsy, 3 = sleepy but arousable toverbal commands, 4 = sleepy but arousable to moderate stimulus, 5 = unconscious.

The primary outcome of this study, analgesic efficacy of transdermal buprenorphine in postoperative period was evaluated by comparing the timing of first rescue analgesic and total dose of postoperative rescue analgesic requirement in 5 days between the two groups. Associated haemodynamic changes and safety of transdermal buprenorphine were also assessed by monitoring any untoward side effect such as nausea, vomiting, sedation and respiratory depression during the study as a secondary outcome.

RESULTS

The demographic and clinical characteristics were comparable between the two groups.

Table 1. Demographic and clinical characteristics

Parameter	Group B [n=30]	Group P [n=30]	P value
Age in yrs	41.7 ± 9.3	41.3 ± 8.9	.854
BMI [kg/m2]	26.2 ± 2.8	25.0 ± 2.6	.101
Male: Female[n%]	16[53.3]:14[46.7]	16[53.3]:14[46.7]	1.000
ASA 1: ASA 11 [n%]	17[56.7]:13[43.3]	16[53.3]:14[46.7]	.795
Surgery duration [min]	92.5 ± 30.0	81.8 ± 23.3	.130
Surgery type Lumbar disc: Cervical disc	21:9	21:9	1.0

Timing of first rescue analgesic requirement was significantly earlier in placebo group patients [61.3 ± 22.9min] in contrast to buprenorphine group [743.9± 20.2min] (P < 0.001) .

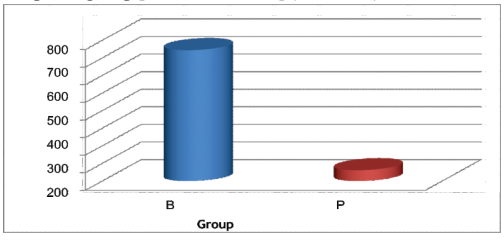

Fig 1 : Time to first dose of rescue analgesic

The frequency and total dose of post-operative tramadol requirement were also significantly higher in placebo group [326.6 ± 69.1 mg tramadol] in contrast to buprenorphine group [116.6 ± 64.7 mg tramadol] *(P < 0.001)* .Of the 30 patients in buprenorphine group, 4 (13.33%) did not require any rescue analgesics, 9 (30%) required twice and the rest (56.6%) required a single dose of rescue analgesic during the study. In the placebo group, all patients required rescue analgesic, 4-5 times during the study period.

All patients in buprenorphine group maintained stable intraoperative hemodynamic status and did not require any additional dose of IV fentanyl intraoperatively. In placebo group most of the patients (60%) received additional doses of intraoperative fentanyl to control the haemodynamic surges.

Table 2. Requirement of additional dose of intraoperative fentanyl.

INTRAOPERATIVE FENTANYL	Group B	Group P
YES	0	12
NO	30	18
TOTAL	30	30

VAS scores were significantly lower in the buprenorphine group. None of the patients in the buprenorphine group were excessively sedated. There was no incidence of post-operative hypoxia, respiratory depression, significant bradycardia or hypotension in the buprenorphine group.

SIDE EFFECTS

The buprenorphine patch was well tolerated by the study group. Nausea and vomiting were the only side effects reported.

Table 3. Side effects

Complication	TDB group n [%]	TDP group n [%]
Nausea	5 [16.7]	7 [23.3]
Vomiting	1 [3.3]	1 [3.3]
Constipation	0	0
Application site rash	0	0
Head ache	0	0
No complication	24 [80]	22 [73.3]

DISCUSSION

Transdermal buprenorphine patch is increasingly used in chronic pain management. However its role in acute post operative pain is not well established. Few studies using transdermal buprenorphine patch for acute post-operative pain management have also used the 10mg patch and found it to be effective with minimal incidence of PONV[5,6]. The median time for transdermal buprenorphine 10 µg/hour to deliver quantifiable buprenorphine concentrations (≥ 25 pg/mL) is approximately 17 hrs[7]. Hence in our study, buprenorphine patch was applied 20 hrs before surgery. Niyogi S et.al.[5], in a similar study , also had applied the buprenorphine patch 20 hrs before surgery. Peak plasma concentration is attained by 48-72hrs and steady state concentration by 72 hrs after the application of transdermal buprenorphine 10mg patch.[7] In a study by Kadapamannil et al.[6] applying buprenorphine patch 10 mg, 72 hrs preoperatively resulted in better post op analgesia than when the patch was applied 48 hrs preoperatively . But patients in both the groups were predisposed to side effects like nausea, vomiting and sedation with early preoperative application of the patch, even when they didn't have any associated pain. In our study ,VAS score was used for assessment of post op analgesia. The use of VAS score do not account for subjective variations in pain perception. Periodic estimation of plasma concentration of buprenorphine could have given a definite idea regarding the efficacy of drug absorption, time to peak plasma concentration and steady state plasma concentration following transdermal administration of the drug. Patches were applied only 20 hrs before surgery while it takes 48 hrs to reach peak plasma drug levels and 72 hrs to reach steady state plasma levels. The use of opioids via PCA pumps for the initial 12 – 24 hrs could have given better analgesia in the immediate post- operative period similar to the the study by Ho-Joong Kim et al.[8] Future studies with bigger sample size, including estimation of plasma buprenorphine levels is needed to establish the definitive role of transdermal buprenorphine in acute postoperative pain management and to determine the optimal time of preoperative application of the patch to obtain maximal pain relief in the early post- operative period.

CONCLUSION

Transdermal buprenorphine patch 10 µg/hr is effective in prolonging post- operative analgesia when applied 20 hrs before the surgery. Hence it can be one of the important components of multimodal analgesia in acute postoperative pain management in adult patients. By providing sustained and continuous background analgesia it can significantly reduce postoperative rescue analgesic requirement. The patch is safe for use in acute post-operative setting maintaining stable hemodynamics without causing any hypoxia or respiratory depression. The patch is generally well tolerated with minimal side effects like nausea and vomiting.

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