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Original Research Article

Comparative evaluation of analgesic efficacy of buprenorphine transdermal patch and fentanyl transdermal patch in the management of postoperative pain after lower limb surgery

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ABSTRACT

Background: Postoperative pain represents a significant medical issue that needs immediate attention. Despite advancements in pain management, managing postoperative pain remains challenging. Transdermal drug delivery systems (TDDS) offers a straightforward, reliable, non-invasive, and patient-friendly approach for alleviating post-surgical pain. Hence, this study was planned to evaluate the analgesic efficacy of buprenorphine and fentanyl transdermal patch in the management of post-operative pain after lower limb surgery.
Methods: In this prospective, randomised study, 82 adult patients of either sex undergoing elective lower limb surgery were randomly allocated into two groups- Group A (Transdermal Buprenorphine 20 mg patch) and Group B (Transdermal Fentanyl 50 mcg patch). Postoperative pain was assessed by 10-point Visual Analogue Scale (VAS) every 6 hours following surgery on the first day and then daily for next 4 days. All patients were also monitored for total rescue analgesic requirement, drug-related adverse effect and haemodynamic status. Statistical analysis was carried out using student *t*-test and Chi-square test. A p-value <0.05 was considered significant.
Results: The mean pain intensity scores were found to be significantly different (p<0.0001) between the two groups, with VAS scores consistently lower in Buprenorphine group as compared to Fentanyl group. Also, Buprenorphine group had the lowest demand for rescue analgesic, with 58.5% of patients requiring two administrations and 36.6% needing only one. Patients belonging to Fentanyl group exhibited higher occurrence of nausea (46.3%), vomiting (46.3%) and pruritus (31.7%).
Conclusions: Our study concludes that transdermal patch of buprenorphine demonstrates superior efficacy and safety profile as compared to fentanyl patch for post-operative pain management in lower limb surgeries.

Keywords: Buprenorphine, Fentanyl, Post-operative pain, Rescue analgesia, Transdermal patch

INTRODUCTION

Postoperative pain poses a significant medical issue for the patient undergoing surgery. Globally, innumerable surgeries are performed every year, but incidence of postoperative pain is still widespread.[1] Around 80% of patients undergoing surgery suffer from an acute postoperative pain and most of them report worsening of pain intensity from moderate to severe.[2] Postoperative pain is responsible for delayed patient recovery, prolonged hospital stay, increased health care cost and patient dissatisfaction.[3,4] Off late pain relief has been recognised as a 'human right' by World Health Organisation and International association for the study of pain.[3,5] As a result effective control of pain after any surgical intervention is emerging as an important postoperative quality measure.[5] Numerous interventions and management strategies are

available for managing postoperative pain but use of opioid analgesics for pain relief still dominates.[6,7]

In the recent years, postoperative pain management has shown marked improvement by employing transdermal drug delivery system (TDDS). TDDS is a simple, dependable, painless and compliant method for post-surgical pain relief.[8-10] Buprenorphine is a semi-synthetic opioid which acts as partial agonist at μ opioid receptor and a weak antagonist at Kappa opioid receptor. It is 75 to 100 times more potent than that of morphine.[11-13] Fentanyl is a synthetic opioid agonist which is 50 to 100 times more potent than morphine. It primarily acts on μ-opioid receptors.[14] Both Buprenorphine and Fentanyl are considered optimum for drug delivery through transdermal patch because of their low molecular weight, high lipid solubility and high potency.[13,14] Hence, this study was planned to evaluate analgesic efficacy of buprenorphine and fentanyl transdermal patch in the management of post-operative pain after lower limb surgery.

METHODS

A prospective, randomised study was conducted from September 2021 to March 2022 at a tertiary care teaching hospital in Indore after obtaining approval from Institutional Review Board (IRB). Patients in the age group of 18-80 years, of either sex, with American society of Anaesthesiologists (ASA) physical status Grade I and II scheduled for elective lower limb surgery under S.A.B (Sub-arachnoid block) and willing to participate were enrolled in the study. Patients with ASA physical status ≥ III, those posted for emergency surgeries, those having history of bronchial asthma, urticaria or any other allergic disorders were excluded from the study. Patients having history of opioid dependence, having known allergy to study drugs or with known contraindications to the use of transdermal patches were also excluded. Likewise, pregnant and lactating women were excluded. Only patients satisfying inclusion criteria were enrolled in the study after obtaining informed consent. A total of 82 patients were randomly allocated into two groups (A and B) using computer generated random tables. Patients of Group A received transdermal buprenorphine 20 mg patch and those of Group B received transdermal fentanyl 50 microgram patch 12 hours before proposed surgery. The patches were applied on intact and healthy skin, ensuring proper adhesion.

All the patients underwent pre-anaesthetic evaluation before surgery. Patients were taken into operation theatre and their baseline hemodynamic parameters such as pulse rate, blood pressure, oxygen saturation, respiratory rate were noted. Standardized monitoring procedures such as electrocardiogram (ECG), pulse oximetry (SPO_2), non-invasive blood pressure monitoring were applied. All the patients were administered S.A.B using 0.5% hyperbaric bupivacaine with 23 or 25 gauge Quincke spinal needle to obtain a sensory block of T8-T10. Pain was assessed by 10 point Visual Analogue Scale (VAS) at the following time periods: 6 hourly for initial 24 hours postoperative pain and then daily for next 4 days. Intravenous paracetamol (1 gram in 100 ml saline) was used as rescue analgesic if VAS score was ≥5. Amount of rescue analgesia as well as time at which rescue analgesia was given were recorded. Hemodynamic parameters were recorded at regular intervals for initial 24 hrs. Adverse effects were also noted.

Data was compiled using Microsoft excel and statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 29.0. Categorical variables were expressed in percentages whereas continuous variables were expressed as Mean±Standard deviation. The Student's t-test was applied for continuous variables and Chi-square test was employed for categorical variables. A p value <0.05 was considered significant.

RESULTS

Total 82 patients were enrolled in the study. The baseline characteristics of patients are given in Table 1. Patient characteristics such as age, sex, ASA grades and BMI were comparable between the two groups. Also, no significant difference was observed between the two groups with regards to their baseline hemodynamic variables such as heart rate, blood pressure, oxygen saturation, respiratory rate and duration of surgery.

Table 1: Patient demographics and clinical characteristics.

Parameter	Group A (n=41)	Group B (n=41)	P value
Age in years (Mean±SD)	44.98±13.543	42.05±11.709	0.298
Sex, male/female	26/15	26/15	1.00
ASA grades I/II	22/19	29/12	0.1108
BMI (Kg/m^2) (Mean±SD)	20.346±1.6538	20.068±1.3839	0.412
SBP (mm of Hg) (Mean±SD)	120.98±11.46	117.66±10.97	0.184
DBP (mm of Hg) (Mean±SD)	76.68±8.82	77±8.59	0.868
Heart rate (Mean±SD)	74.05±12.19	76.29±9.72	0.3604
Respiratory rate (Mean±SD)	13.46±1.73	14.12±1.95	0.1089
SPO2 (Mean±SD)	99.59±0.77	99.56±0.78	0.771
Duration of surgery (mins)	122.34±13.776	120.17±20.422	0.574

(SD- Standard Deviation; ASA- American society of Anaesthesiologists; BMI- Body Mass Index; SBP- Systolic Blood Pressure; DBP- Diastolic Blood Pressure; SPO2- Saturation of Peripheral Oxygen)

Table 2: Comparison of post-operative VAS scores between the two groups.

Time interval	Group A (n=41)	Group B (n=41)	P value
0 hrs	0	0	-
6 hrs	6.12±1.08	7.61±0.77	<0.0001
12 hrs	3.76±0.7	7.00±0.81	<0.0001
18 hrs	4.63±1.28	6.66±0.73	<0.0001
24 hrs	3.27±0.78	5.98±0.94	<0.0001
48 hrs	2.66±0.96	5.44±0.74	<0.0001
72 hrs	1.49±1.08	4.11±0.77	<0.0001
96 hrs	0.95±0.86	2.80±0.71	<0.0001
120 hrs	0.41±0.59	2.32±0.87	<0.0001

Table 2 compare the post-operative VAS scores between the two groups AT different intervals following surgery. At the 0 hr time point, both the groups had a VAS score of 0, which suggests no pain immediately after the surgical intervention. This could be due to residual anaesthesia effect. From 6 hrs onwards, the mean pain scores continued to be consistently low in Group A as compared to Group B and a statistically significant difference was observed in the VAS scores ($p<0.0001$) at all times.

All the patients of Group A as well as Group B needed rescue analgesic. Table 3 exhibits comprehensive analysis of use of rescue analgesia for five days post-surgery. Group A had the lowest demand for rescue analgesic, with 58.5% of patients requiring two administrations and 36.6% needing only one. In contrast, rescue pain relief in 68.3% of Group B patients was obtained by five administrations whereas 31.7% patients needed six administrations.

Postoperatively, patients of both the groups complained of side effects as shown in Table 3. As compared to Group A, patients belonging to Group B exhibited higher occurrence of nausea (46.3%), vomiting (46.3%) and pruritus (31.7%). None of the patient in both groups experienced skin necrosis. Throughout the post-operative period, no significant change in respiratory rate or breathing pattern or any respiratory depression was observed in any of the two groups.

Table 3: Rescue analgesic requirement and side effect profile.

		Group A, N (%)	Group B, N (%)	P value
Number of rescue analgesics required	0	2 (4.9)	0 (0.0)	0.152
	1	15 (36.6)	0 (0.0)	0.0001
	2	24 (58.5)	0 (0.0)	0.0001
	3	0 (0.0)	0 (0.0)	-
	4	0 (0.0)	28 (68.3)	0.0001
	5	0 (0.0)	13 (31.7)	0.0001
Side effects	Nausea	6 (14.6)	19 (46.3)	0.0018
	Vomiting	6 (14.6)	19 (46.3)	0.0018
	Pruritus	0 (0.00)	13 (31.7)	0.0001
	Skin necrosis	0 (0.0)	0 (0.0)	-

DISCUSSION

The prevention and alleviation of post-operative pain is an important responsibility of health care professionals.[5] However, evidence suggests that a considerable population of patients experience poorly managed post-operative pain which increases possibility of delayed recovery, complications, persistent post-surgical pain and high cost of medical care.[15]

Transdermal drug delivery system (TDDS) has emerged as a novel and promising method for post-surgical pain relief. It offers continuous drug delivery and sustained plasma drug levels. Being non-invasive, it also ensures enhanced patient acceptability and compliance.[16] Transdermal formulations of opioids like buprenorphine and fentanyl offer benefits like simplified administration, a favourable safety profile, non-invasive mode of delivering sustained plasma drug levels.[17,18] Fentanyl is a μ opioid receptor agonist which is characterised by low molecular weight, high lipid solubility and high analgesic potency. These attributes make it well suited for effective delivery through skin for pain management.[14,19] On transdermal application, fentanyl, initially accumulates in skin and gradually enters into systemic circulation with a notable delay of 17 to 48 hours before reaching peak plasma concentration. The pain relieving effect can last for as long as three days potentially reducing the need of additional analgesics.[9,20] Buprenorphine is a semi-synthetic partial μ opioid receptor agonist and an antagonist at Kappa opioid receptor. Because of its distinctive pharmacodynamics profile, it exhibits reduced likelihood of opioid related side effects and lower potential of abuse as compared to full μ opioid receptor agonists.[12,21] Moreover, being highly potent, lipophilic compound with low molecular weight, it quickly enters systemic circulation by penetrating the skin through passive diffusion.[22]

In this prospective randomised study, for the management of post-surgical pain, we used transdermal Buprenorphine patch (Group A) and compared it with transdermal Fentanyl patch (Group B). Analysis of demographic

details revealed male predominance in both the groups with total males accounting for 63.41% and females were 36.58%. Moreover, male-female ratio was also comparable. Similar trends have been reported in studies by Arshad et al and Kausar D et al.[9,23] Mean age of patients belonging to Group A and Group B was 44.98±13.543 and 42.05±11.709 respectively and the difference was statistically insignificant. Our findings coincided with other studies by Khandelwal et al and Kausar et al.[18,23] Also, no significant difference was observed in between the two groups for other demographic variables such as BMI and ASA grade.

The baseline hemodynamic variables (SBP, DBP, HR, and SPO2) in both groups were similar and did not demonstrate any clinically significant difference. Similar readings were recorded in some other studies also.[9,18]

In our study, the VAS scores significantly reduced from day 1 to day 5 in patients of Group A as compared to those of Group B. Hence, transdermal buprenorphine patch was found to be more efficient in relieving pain after surgery which is in line with a systematic review by Machado et al and research by Khandelwal et al and Kausar et al.[18,21,23] However, our findings are in contrast with a study by Arshad et al which showed better analgesic effect of transdermal fentanyl patch as compared to transdermal buprenorphine for post-operative pain relief after major abdominal surgeries.[9] Similarly, a systematic review and meta-analysis by Aguilar et al that included 15 randomized controlled trials comparing transdermal buprenorphine with other analgesics or placebo inferenced that there is limited evidence to support that transdermal buprenorphine effectively manages postoperative pain as compared to other analgesics.[24] Twenty four (58.5%) patients of buprenorphine group required two doses of rescue analgesia and 15 patients needed single dose. On the other hand, the need of rescue analgesics was more profound in fentanyl group, with 28 (68.3%) patients requiring five doses and 13 (31.7%) patients requiring six doses. This reinforces our conclusion that transdermal buprenorphine provides superior efficacy as compared to transdermal fentanyl.

In the present study, incidence of adverse effects viz. nausea, vomiting and pruritus was more profound in the fentanyl group as compared to buprenorphine group. Walsh et al, Kausar et al and Khandelwal et al also observed lower incidence of nausea/vomiting and pruritus in buprenorphine group.[18,23,25] Likewise, in another post-marketing surveillance study of transdermal buprenorphine use, among 13179 patients surveyed, only 4% reported nausea and 1.6% reported vomiting.

This study had some limitations. Firstly, this study evaluated efficacy of transdermal patch solely in post-operative patients undergoing lower limb surgeries. This study sample size was limited and plasma drug levels were not measured. Hence, further research with larger sample is needed to assess the effectiveness of transdermal patches in managing pain across other major surgical interventions also.

CONCLUSION

Our study concludes that transdermal patch of buprenorphine has demonstrated superior efficacy and safety profile as compared to fentanyl patch for post-operative pain management in lower limb surgeries. This treatment modality also ensures stable haemodynamics and reduces the need for rescue analgesics.

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