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Comparative Study of Transdermal Patch of Fentanyl with that of Buprenorphine forPostoperative Pain Management in Post thoracotomy Surgery Patients

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Abstract

Background: Pain after thoracotomy is probably the most severe pain experienced by the patients and Opioids are one of the most commonly used analgesics for postoperative pain. A transdermal drug delivery system is used to provide steady and continuous drug delivery

Aim: To compare the efficacy and safety of 25 mcg/hour of fentanyl patch with 10mcg/hour of buprenorphine patch for postoperative pain management in post Thoracotomy patients.

Materials and methods: Total forty patients of ASA Grade I, II and III, age between 20 and 60 years, who have undergone thoracotomy surgeries were included in this study and were randomly divided into two groups of 20 patients in each group. Group A received 25 mcg/hour of fentanyl patch and Group B received 10 mcg/hour of Buprenorphine patch immediately after patient was received in critical care unit post-surgery. Patients were followed for three days.

Results: Demographic profile and baseline characteristics are comparable between two groups. Group A had significantly higher level of mean VAS

score as compared to that of Group B at Day 2 and 3. In the same follow up period, both the groups were comparable in regards to hemodynamic variables (HR, SBP and DBP) and mean level of sedation score. In Group A, 7 (36.66%) patients and in Group B, 5 (26.66%) patients required single dose of rescue analgesic, (*p* - value > 0.05). The incidence of nausea and vomiting were 13.33% in Group A and 23.33% in Group B.

Conclusion: Both the fentanyl and buprenorphine patch are effective and safe in controlling pain postoperatively but buprenorphine is better than fentanyl in these respects, as it have longer duration of action and also require less rescue analgesic for pain relief.

Keywords: Analgesics; Opioids; Transdermal; Patch; Fentanyl; Buprenorphine; Thoracotomy

Introduction

Cardiovascular thoracic surgeries will include Thoracotomy or thoracoscopy procedures. Thoracotomy incision will cause impaired pulmonary function and chest pain postoperatively. This pain originates from pleural and muscular damage, costovertebral joint disruption, intercostals nerve injury during surgery. Thus, postoperative pain relief is an essential aspect of critical care management in these patients as it affects the quality of patient recovery and resulting postoperative morbidities. Adequate pain management leads to early mobilization, improves respiratory function and reduces postoperative complications.

At present, various analgesic modalities are available for postthoracotomy pain management including thoracic neuraxial blocks and indwelling catheters, intercostal nerve blocks, patient-controlled analgesia, oral, parenteral and transdermal NSAIDs and parenteral or transdermal opioids. Among these modalities transdermal opioid delivery is advantageous as it avoids the peaks and troughs of intermittent dosage which may lead to various side effects like sedation, nausea, vomiting and respiratory depression. The fentanyl patch is one of the great commercial success in transdermal drug delivery. Buprenorphine is a synthetic opioid analgesic used in a variety of therapeutic situations for the relief of moderate to severe pain. Hence, the present study was carried out to compare transdermal fentanyl and transdermal buprenorphine for postoperative pain relief.

Materials and Methods

After obtaining approval from Institutional Ethics Committee and informed consent from patients, this prospective randomized study was conducted in 40 patients between August 2021 – July 2022 at Alluri Sitarama Raju Academy of Medical Sciences, Eluru

Inclusion criteria

Patients aged between 20 and 60 years and of either sex.ASA Grade I, II and III and weight 40–80 kg.

Patients who have undergone thoracotomy surgeries.

Exclusion criteria

Patients < 20 years and > 60 years of age

Patients with ASA Grade IV

Patients with known Opioids allergy or dependence in the past, skin infection and sensitive skin Patients with impaired pulmonary functions, weight less than 40 kg and more than 80 kg Patients own refusal for participation were excluded from the study

Patients were divided based on computerized randomization into two groups of 20 patients each. Group A received 25 mcg/hr of fentanyl patch and Group B received 10 mcg/hour of buprenorphine patch immediately after patient received in critical care unit post-surgery.

A detailed pre-Anaesthetic checkup was done. Patients were taken up for surgery after adequate starvation of 8 hrs. In the operation theatre, intravenous access was established. All noninvasive monitoring was attached including pulse oxymeter, SpO2 and NIBP. Patients were premedicated with glycopyrrolate 4mcg/kg ondansetron 0.1 mg/kg IV and sedated with midazolam 0.03 mg/kg IV and fentanyl 2mcg/kg IV. After preoxygenation for 3 mins general anesthesia was induced with propofol 2 mg/kg and after ensuring adequate mask ventilation patient was paralyzed with 0.1mg/kg vecuronium and trachea was intubated with portex endotracheal tube of 7.5 mm ID for females and 8.5 mm ID for males. After ensuring correct placement with end tidal CO2 and proper positioning of the tube, positive pressure ventilation was initiated. Anaesthesia was maintained with a mixture of 50% O2 and nitrous oxide mixture and Isoflurane (MAC 1 to 1.2) with 0.08-0.12mg/kg/hr vecuronium infusion. An arterial line was then be secured for invasive arterial blood pressure and heart rate monitoring. After completion of procedure patient was shifted to critical care unit sedated and paralyzed with assisted ventilation and continuous infusions of the relaxant and other intraoperative drugs required.Patient was put on ventilator, all monitors attached including pulse oximeter, ECG, arterial blood pressure and temperature. After confirming the vital parameters to be normal transdermal opioid patch was applied on clear hair free area of upper arm or chest or back. Along with their routine drugs Inj. Paracetamol TDS and Inj. Tramadol bd was continued for 24 hours post-surgery. As the peak levels of transdermal opioids were attained after 12–24 hours, the analgesia was covered with parenteral NSAIDs and opioids. Patient was gradually weaned over 12 hours and extubated after serial arterial blood gas monitoring and patients' response in terms of sensory and motor activity. After extubation, pain was assessed using visual analog scale whereas sedation scoring was done according to Ramsay Sedation Scale. Continuous hemodynamic monitoring was done. The requirement of rescue analgesics after 24 hours was noted. In case of any side-effects related to the patch, the patch was removed and discontinued. All monitoring and findings were noted for three days postoperatively. In case of any complications were noted and managed accordingly. If not fulfilling the criteria for study, patient was excluded from study.

Statistical Analysis

The data from both the groups was collected and compared statistically using student *t*-test /Fischer-exact test. Statistically significant differences between two groups are detected by keeping $\alpha = 0.05$ and power of study 95%.

Observations and Results

Total 40 patients were included in the study, among them 26(65%) were males and 14 (35%) were females. The demographic profile of the patients and baseline characteristics were comparable between two groups and found no statistically significant difference ($p > 0.05$) as shown in (Table 1).

Characteristics		**Group A**	**Group B**	**p - value**
Age in years		43.5 ± 10.52	42.73 ± 13.49	0.807
Sex, No. (%)	Male	14 (70%)	12 (60%)	–
	Female	6 (30%)	8 (40%)	–
ASA Grade, No. (%)	I	12 (60%)	11 (55%)	–

	II	8 (40%)	9 (45%)	–
Heart Rate		87.13 ± 7.46	88.73 ± 8.32	0.436
SBP		126.56 ± 4.87	126.76 ± 8.31	0.909
DBP		82.4 ± 7.07	81.1 ± 7.60	0.495
SpO2 (%)		98.96 ± 0.96	99 ± 0.98	0.894
VAS		4.4 ± 0.81	4.4 ± 0.81	1
Sedation Score (RSS)		1.96 ± 0.31	1.93 ± 0.25	0.656

Table 1: Comparison of demographic profile

Table 2 shows, the mean values of VAS from Day 2 and Day 3 in both groups. Group A had significantly higher level of mean VAS score as compared to Group B during the follow up period. At day 2 and day 3 the difference was highly significant.

In Group A, 7 (36.66%) patients and in Group B, 5 (26.66%) patients required single dose of rescue analgesic. The difference in rescue analgesic requirement was not statistically significant (p- value > 0.05).

Follow-up day	Group A	Group B	P - Value
Day 2	1.86 ± 1.16	0.2 ± 0.61	< 0.0001
Day 3	2.2 ± 0.96	0.2 ± 0.61	< 0.0001

Table 2: Day1 – Day 3 VAS Variations

At day 1, 2 and 3, both the groups were comparable in regards to mean level of sedation score, Table 3 shows the variation in sedation score from day 1 to day 3 and no statistically significant difference found among two groups. The incidence of nausea and vomiting were 13.33% in Group A and 23.33% in Group B. One patient in Group A had itching

Follow-up day	Group A	Group B	p-value
Day 1	1.96 ± 0.18	1.96 ± 0.18	1
Day 2	1.96 ± 0.18	2.00 ± 0.00	0.32
Day 3	2.00 ± 0.26	2.00 ± 0.00	1

Table 3: Variation in Sedation score from day 1 to day 3

Discussion

Thoracotomy is considered the most painful of surgical procedures and providing effective analgesia is one of the challenges for all anesthetists.

In post-thoracotomy patients analgesia can be administered as boluses or continuous infusion with pharmacokinetic and patient-controlled systems like PCA (Patient Controlled Analgesia), Target Control Infusion (TCI) and a new approach of PMA (Patient Maintained Analgesia).

The use of adhesive skin patches (Transdermal Drug Delivery Systems-TDDS) to deliver drugs systemically for postoperative analgesia is a relatively new phenomenon and for that opioids (morphine, fentanyl, pethidine, buprenorphine and tramadol) have been the mainstay of postoperative analgesia.

Fentanyl permeation in human skin samples in scientific literature was first reported in seminal paper by Michaels et al. Transdermal route for fentanyl delivery suitability was examined further by Roy and Flynn. Transdermal fentanyl first patch was approved by FDA in 1990s. Fentanyl patches are designed to deliver fentanyl at four constant rates as 25, 50, 75, and 100 µg/ hr for a period of 72 hours. After initial application, a depot of fentanyl forms in the upper skin layers and serum fentanyl concentrations increase gradually, generally leveling off between 12 and 24 hours.

The steady-state serum concentration is reached after 24 hours and maintained as long as the patch is renewed.

Variations were noticed in serum fentanyl concentration during the 72-h period; concentrations tend to be higher in first 24hrs and lowered on second and third day due to decreasing concentration gradient between patch and skin. Fentanyl delivery is not affected by local blood supply, but an increase in body temperature up to 40°C can increase absorption rate.

Similarly, transdermal application of buprenorphine meets all the requirements for successful treatment of chronic pain. Buprenorphine is a partial agonist at the μ receptor and its analgesic efficacy is comparable with the usual doses of other opioids such as pentazocine, morphine and pethidine. In India, buprenorphine patches are available in three different strengths as 5, 10, 20μ g/h.

Each transdermal patch usually contains 5 mg of buprenorphine in 6.25 cm2 area releasing 5 μg of buprenorphine per hour over a period of 7 days. Patches with higher strengths have proportionately larger areas. After application, these are usually kept for 7 days. More than one patch may be applied depending on the need, but the total dosage should not exceed 20μ g/h as prescribed by FDA.

In the present study, we compared 25 mcg/hourof fentanyl patch with 10 mcg/hour transdermal buprenorphine patch for postoperative pain relief in post Thoracotomy patients.

There was no statistically significant difference found between two groups in regards to demographic profile and baseline characteristics as similar to the study done by Arshad et al.

In Group B the VAS score was significantly lower than Group A on day 2 and 3. The potency of fentanyl in form of transdermal patch is very good and able to maintain VAS score around 2. As mentioned in previous studies it is comparable. But when compared to the VAS score of buprenorphine patch which is mostly 0, buprenorphine patch 10 mcg/hr seems to be far better.

Thus, the result of VAS score in this study suggested that both the patches were effective in controlling postoperative pain but buprenorphine was better in this regard.

Fentanyl patch had duration of action of 3 days while buprenorphine patch had duration of action of 7 days. Therefore, buprenorphine provides longer pain relief as compared to fentanyl but the latter is more effective analgesic.

In Group A, 7 patients and in Group B, 5 patients were required single dose of rescue analgesic. Further, this finding resolved that buprenorphine patch is better analgesic than fentanyl patch.

Sedation scores and hemodynamic variables in both groups were comparable. None of the

patient in our study showed excessive sedation or respiratory depression. All patients were calm, comfortable and easily arousable throughout the study period. The sedation scores were slightly increased in Group B as compared to baseline but in Group A, sedation score were same at day 1, 2, and slightly increased at day three as compared to baseline.

Thus, buprenorphine patch provides more sedation than fentanyl patch but this difference was not statistically significant.

There are isolated case reports of bradycardia with the use of fentanyl TDS but in current study, we did not found any adverse hemodynamic events in either group. Nausea and vomiting were main side-effects of the opioid drugs.

The incidence of nausea and vomiting were 13.33% in Group A and 23.33% in Group B, this is significantly lower than observed in previous studies.

Conclusion

The transdermal fentanyl 25 mcg/h and transdermal buprenorphine 10 mcg/h are safe and effective for postoperative pain relief in post thoracotomy patients but the buprenorphine is better than fentanyl in this respect and can be used for 7 days.

However, Fentanyl is more cost-effective and is preferred for postoperative pain management more often but with this study we would like to use buprenorphine patch for post operative pain management in post thoracotomy patients as it has longer duration of action.

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