Original Research Article

Comparative study between Buprenorphine and Fentanyl transdermal patch to evaluate post-operative pain relief after cardiac surgery: A randomized control trial study

Vijay Harischandra Patil[1], Bhagyashree Inkane[2], Dipakkumar Hiralal Ruparel[3*], Subin Thomas[4]

[1]Assistant Professor, Department of Anaesthesia, Government Medical College, Nagpur, Maharashtra, India
[2]Senior Resident, Department of Anaesthesia, Government Medical College, Nagpur, Maharashtra, India
[3]Associate Professor, Department of Anaesthesia, Government Medical College, Medical Square, Gondia, Maharashtra, India
[4]Senior Resident, Department of Anaesthesia, Government Medical College, Nagpur, Maharashtra, India

Received: 25-11-2021 / Revised: 28-12-2021 / Accepted: 07-01-2022

Abstract

Introduction: Pain due to thoracotomy creates greatest demand for postoperative analgesia. Multimodal analgesia with various routes can be of great help to fulfill demands of analgesia in these patients. Opioids given by transdermal route offers newer modality of management with potential benefits of being noninvasive, sustained blood levels and bypasses first pass metabolism. We aimed to evaluate efficacy of Buprenorphine and Fentanyl Transdermal patch for post-operative pain relief after cardiac surgery. **Methods:** It was prospective, randomized, double-blind study in which 60 adult patients undergoing cardiac surgery were randomly segregated into two groups. **Group A:** 30 patients received Buprenorphine transdermal patch (10mcg/hr) and **Group B:** 30 patients received Fentanyl transdermal patch (50mcg/hr) 12- 24 hours prior to extubation. Analgesia was assessed using VAS score along with hemodynamic parameters and adverse effects. **Results:** Demographic parameters, baseline hemodynamics and perioperative hemodynamics were comparable. Baseline VAS score was comparable in two groups however statistically significant difference in two groups in VAS was observed thereafter till 72 hours. VAS score was higher in group A as compared to group B at the time of removal of ICD. 3 (10%) and 2 (6.7%) patients in Group A and Group B respectively required rescue analgesic which was not significant. Time for requirement of first rescue analgesic was significantly longer in Group B compared to Group A ie767.13 ± 73.59 minutes vs. 1224.37 ± 39.37 minutes. Adverse effects were comparable in two groups. **Conclusion:** Fentanyl and Buprenorphine TDDS are effective in postoperative analgesia in cardiac surgical patients. However Fentanyl TDDS has better analgesia.

Key words: Fentanyl, Buprenorphine, transdermal patch, Cardiac surgery, pain.

Introduction

Pain after cardiac surgery is most severe during the first 24 hours and decreases on subsequent days, because it is a "self-limiting" phenomenon. Pain is the most severe in patients after open thoracic surgery. Patients undergoing surgery with the use of cardiopulmonary bypass report slightly higher pain intensity than those in whom extracorporeal circulation is not used[1]. Extracorporeal circulation is essentially associated with the induction of the systemic inflammatory response syndrome, with potential end-organ dysfunctions. Postoperative pain management is crucial, as inadequately controlled pain delays rehabilitation, prolongs the duration of treatment and worsens the patient's quality of life[2].

The development of a novel delivery system for existing drug molecules not only improves the drug's performance in terms of efficacy and safety but also improves patient compliance and overall therapeutic benefit to a significant extent[3]. Transdermal Drug Delivery System (TDDS) are defined as self-contained, discrete dosage forms which are also known as "patches"[4,5] when patches are applied to the intact skin, deliver the drug through the skin at a controlled rate to the systemic circulation. TDDS are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin.

Hence the present study was done to compare Buprenorphine and Fentanyl Transdermal patch for post-operative pain relief after cardiac surgery, assess the total dose of rescue analgesic and adverse effects if any.

*Correspondence
Dr. Dipakkumar Hiralal Ruparel
Associate Professor, Department of Anaesthesia, Government Medical College, Medical Square, Gondia, Maharashtra, India

Methods

After obtaining approval from institutional ethics committee and written informed consent from patients, this randomized double blinded study was conducted in tertiary care centre during the period of January 2019 to September 2020 on 60 patients undergoing cardiac surgery through median sternotomy incision. The clinical research was done following the ethical principles for medical research involving human subjects in accordance with the Helsinki Declaration 2013.

Patient of age group 18 to65 years posted for elective cardiac surgery procedure were included in study while those patient refusing to give consent, allergic to study drugs and with hepato-renal co morbidities were excluded from study.

All patients were investigated according to institutional protocol. Patients were randomly allocated to two groups using computerized generation random allocation plan.

Group A: 30 patients received Buprenorphine transdermal patch (10mcg/hr) on hairless area of chest, back, flank and upper arm.

Group B: 30 patients received Fentanyl transdermal patch (50mcg/hr) on hairless area of chest, back, flank and upper arm.

All baseline and special investigations of patients were recorded. On arrival to OR, patients were enquired about NPO status and multipara monitors including Blood pressure (BP) cuff, ECG, Pulseoxymeter(SPO2) were attached and baseline reading of systolic BP(SBP), diastolic BP(DBP) , Mean BP(MAP), SPO2 and heart rate (HR) were recorded. Intravenous access was achieved with 20G intra-venous cannula. At the time of surgery patients were premedicated with inj. Midazolam 1 mg IV and inj. Fentanyl 2 mcg/kg IV after

which arterial line was established. Patients were induced with inj. Propofol 2 mg/kg IV and intubated using inj. Vecuronium 0.1 mg/kg IV after which pulmonary artery catheter was introduced. Anaesthesia was maintained with oxygen, inhalational agents and muscle relaxants to be maintained with Vecuronium, Midazolam, and Fentanyl through infusion. Patients were neither reversed nor extubated and shifted to ICU for elective ventilation support. Patients were extubated after extubation criteria was fulfilled and was usually done after 24 hours of surgery. Transdermal patch was applied to patients 12 to 24 hours prior to extubation. Analgesia was assessed using Visual Analog Scale(VAS) score as primary outcome and total number of rescue analgesia doses respectively for the next 3 days, at 8 hourly intervals. VAS was assessed at the time of ICD removal which was usually removed on day 3.

Hemodynamic parameters and any adverse effects were noted. If the VAS score was 5, then inj. Fentanyl (10 mcg IV) was used as a rescue analgesic.

Primary outcome measured were pain scores at hourly interval in both groups, time for rescue analgesia, total dose of rescue analgesia and vas scores at the time of removal of ICD. Secondary measures were hemodynamic parameters and adverse effects including nausea, vomiting and respiratory depression.

Statistical Analysis

The sample size was calculated in order to be able to detect a reduction of 30% in VAS, with an alpha risk of 5% and a beta risk of 20%, giving a total of 30 participants required per group. All data collected was entered in Microsoft Excel worksheet, and graphs were formed using the same. The quantitative variables (MAP, HR, and Fentanyl consumption) were expressed in terms of mean and standard deviation. The categorical variables (proportions of patients experiencing side effects) were expressed in terms of frequency and percentages. Median and Interquartile range were calculated for nonparametric data All analyses were performed using STAT 11 statistical software (Stata Corp LP, College Station, Texas, USA).

Results

Table 1: Demographic characteristics of the patients

Parameters	Group A	Group B	P value
Age (years) Mean ± SD	49.67 ± 13.84	50.53 ± 12.29	>0.05
Sex Male: Female N(%)	19(63.3%):11(36.7%)	21(70%):9(30%)	>0.05
BMI(Kg/m^2) Mean ± SD	24.70 ± 4.31	25.09 ± 4.50	>0.05

Table 2: Comparison of baseline hemodynamic parameters between groups

Baseline Hemodynamic parameters	Group A Mean ± SD	Group B Mean ± SD	P value
HR (per min)	81.20 ± 5.79	81.90±5.56	>0.05
SBP (mmHg)	136.13± 5.35	134.40±6.00	>0.05
DBP (mmHg)	80.47 ± 8.67	81.43 ± 8.72	>0.05
PASP (mmHg)	18.27±1.41	16.27 ± 1.66	>0.05
PADP (mmHg)	8.17 ±1.37	6.13 ± 1.25	>0.05
RR/minute	18.33 ±1.27	16.33 ± 1.30	>0.05

Where HR – heart rate; SBP – systolic blood pressure; DBP – diastolic blood pressure; PASP – pulmonary artery systolic pressure; PADP – pulmonary artery diastolic pressure; RR – respiratory rate.

The baseline characteristics of the patients are given in the [Table1 and Table2] and were comparable

Table 3: Comparison of VAS score at various postoperative time intervals

Time intervals (in hours) post-extubation	VAS score Group A Mean ± SD	VAS score Group B Mean ± SD	P value
0 hour (after extubation)	3.57± 0.63	3.43± 1.19	>0.05
8 Hours	4.60± 0.67	3.27± 1.14	**<0.05**
16 Hours	4.47 ±0.57	3.10 ±1.09	**<0.05**
24 Hours	4.40 ±0.62	2.83±0.83	**<0.05**
32 Hours	3.87± 0.9	2.67± 0.99	**<0.05**
40 Hours	3.67± 0.8	2.63± 0.85	**<0.05**
48 Hours	3.63 ±0.72	2.37± 0.72	**<0.05**
56 Hours	3.53± 0.63	1.57± 0.63	**<0.05**
64 Hours	3.47 ±0.57	1.53 ± 0.63	**<0.05**
72 Hours	3.40 ±0.56	1.47± 0.67	**<0.05**

Where VAS – visual analog scale

As seen from table 3 baseline VAS score was comparable in two groups however statistically significant difference in two groups was observed thereafter till 72 hours.

Table 4: Comparison of VAS score at the time of removal of ICD

VAS score at time of removal of ICD	Group A Mean ±SD	Group B Mean ±SD	P Value
	2.47 ±0.68	1.40±0.56	<0.05

VAS score was also higher in group A as compared to group B at the time of removal of ICD (Table 4).

Hemodynamic variables in both groups (SBP, DBP, HR PASP, and PADP), shows comparable values in both groups and no significant difference was observed.

The incidence of adverse effects including incidence of nausea, urinary retention and constipation were comparable in both groups. None of the patient in both group experienced skin irritation and respiratory depression.

3 (10%) and 2 (6.7%) patients out of 30 in Group A and Group B respectively required rescue analgesic. This difference in rescue analgesic requirement is not quiet statistically significant (p-value> 0.05).

Discussion

Despite so much development in pain management, approximately 20 to 40% patients tend to suffer from moderate to severe surgical pain especially so after abdominal, thoracic, pelvic and orthopedic surgeries. This postsurgical pain can delay in ambulation, increases cardiopulmonary and thrombotic complications and can lead to chronic pain development[6,7].

Although multimodal analgesia is considered as best modality for postoperative pain , opioids still remains cornerstone in the management of moderate to severe acute postoperative pain[8].

Various routes of administration of analgesics are used by anesthesiologist with each one having its own advantages and adverse effects. Intravenous and oral routes commonly employed method in early postoperative pain, comes with its own adverse effects along with lack of sustained effects. Transdermal patches are becoming increasingly popular for management of acute postoperative pain in orthopedic surgeries and abdominal surgeries due to its high efficacy and longer duration of action[9,10,11].

TDDS provides convenient and safer alternative to oral and parental preparations by avoiding multiple dosing and skin punctures thereby improving patient's compliance too. It provides sustained and continuous plasma concentration of drug and avoids intermittent fall I plasma concentration of drug thereby providing stable plasma concentration of drug which reduces incidence of breakthrough pain and hence the requirement of rescue analgesics. it avoids sudden surge in plasma concentration of drug thereby avoiding side effects , although few side effects like gastrointestinal side effects remain same as those of oral preparations[12,13].

Fentanyl , a potent synthetic opioids analgesic with high lipid solubility and low molecular weight, is suitable for TDDS. It can provide 25 to 100mcg/hour of drug. It takes time to reach peak plasma level and may take up to 1.2 to 40 hours with analgesic effect lasting for 3 days.. Slower onset and large patient to patient variation along with attendant risk of respiratory depression caused many anesthesiologists to consider it as less suitable option for acute pain. Various adverse effects include nausea (36.0%), somnolence (30.2%), vomiting (25.6%), constipation (16.3%), pyrexia (12.8%) and insomnia (10.5%). and respiratory depression (4%)[14,15].

Buprenorphine, a semi synthetic opioids and partial mu receptor agonist, has high lipophilicity and low molecular weight which makes it suitable to use via transdermal route. Most of TDDS of Buprenorphine achieve therapeutic plasma concentration on third day with onset of action within 12 to 24 hours with duration of action lasting for 3 to 7 days[16,17,18].

Buprenorphine has less analgesic tolerance and dependency, has ceiling effect on respiratory depression, less incidence of cognitive dysfunction and other opioids related side effects, has safety profile in elderly and those with renal dysfunction with lack of imunosupression and hypothalamic-pituitary-adrenal pathway side effects[19,20].

The efficacy of both drugs have been studied individually for the management of acute and chronic pain but hardly there are any studies comparing the two opioids. In our study we compared analgesic efficacy of TDDS of both opioids for postoperative pain and requirement of rescue analgesia. The incidence of adverse effect was also studied with each drug.

TDDS system for Fentanyl and Buprenorphine acts for 3 days and 7 days respectively and usually pain severity is of moderate to severe duration up to 72 hours after surgery. Hence we evaluated efficacy of Fentanyl and Buprenorphine TDDS for 72 hours postoperatively[21,22].

Keeping in mind the onset of action of opioids TDDS is 12–24 h, patches were applied 12-24 hours prior to expected time of extubation.

In our study, demographic data was comparable in two groups so also the baseline hemodynamic parameters (Table 1 and 2). The hemodynamic variables in both groups were comparable and did not show any clinically significant deviation from the baseline values. We did not report any isolated incidence of Bradycardia and hypotension as reported by previous study[23].

VAS score, used to assess pain in postoperative period, was significantly lower in Fentanyl group as compared to Buprenorphine group and was consistently lower from 24 hours to 72 hours of extubation. Although VAS score was comparatively higher in Buprenorphine group, still it was not much greater so as to require additional analgesia indicating Buprenorphine was also able to give good pain relief postoperatively though less effective than Fentanyl. Hence we can say that both drugs were effective in postoperative pain although Fentanyl TDDS had better effect.

We also compare VAS score of the patients at the time of removal of ICD which was usually removed on day 3 in our institute. As seen from table 4 VAS score was significantly lower in Fentanyl group than in Buprenorphine group. 3 (10%) and 2 (6.7%) patients in Group A and Group B respectively required rescue analgesic which was statistically not significant. Although time for requirement of first rescue analgesic was significantly longer in Group B compared to Group A ie767.13 ± 73.59 minutes vs. 1224.37 ± 39.37 minutes and was statistically significant.

Patients in both groups were calm and comfortable but were arousable although we did not compare sedation scores in both groups. (6.7%) and 1 (3.3%) patient in Group A had nausea and vomiting respectively while 3 (10%) and 1 (3.3%) patient in Group B had nausea and vomiting respectively and was not significant statistically. None of the patient in both groups experienced respiratory depression. Most studies in the systematic review show no increase in adverse drug reaction as concluded by systemic analysis by Machado FC *et al*[24].However when Buprenorphine was used in higher doses ie 40 μg·h-1 in study conducted by Tassinari *et al*., had greater incidence of nausea and vomiting[25].

Limitations of our study were small group of study population and that too restricted to cardiac surgical patients only. Also we did not measure plasma drug levels and VAS scale is subjective.

Conclusion

We can conclude that both Fentanyl and Buprenorphine TDDS were effective in postoperative analgesia in cardiac surgical patients with fewer side effects and good hemodynamic stability. However Fentanyl TDDS has better analgesia as compared to Buprenorphine TDDS.

References

1. Fot EV, Izotova NN, Yudina AS et al. Automated weaning from mechanical ventilation after off-pump coronary artery bypass grafting. Front Med (Lausanne) 2017;4:31.
2. Braun LA, Stanguts C, Casanelia L et al. Massage therapy for cardiac surgery patients: a randomized trial. J Thorac Cardiovasc Surg. 2012;144(6):1453–1459.
3. Jalwal P, Jangra A, Dhaiya L et al. A review on transdermal patches. Pharm Res. J. 2010; 3:139-149.
4. Bhowmik D, Chiranjib, Chandira M et al. Recent advances in transdermal drug delivery system. Int. J Pharm Tech Res. 2010; 2(1):68-77.
5. Kumar A, Pullankandam N, Prabhu SL et al. Transdermal drug delivery system: an overview. Int. J Pharm Sci. Review Res. 2010;3(2):49-54
6. Gerbershagen HJ, Aduckathil S, Van Wijck AJM, et al. Pain intensity on the first day after surgery: a prospective cohort study comparing 179 surgical procedures. Anesthesiology.2013;118:934---44.
7. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet. 2006;367:1618---25.3
8. Chou R, Gordon DB, De Leon-Casasola OA, et al. Management of postoperative pain: a clinical practice guideline from the Amer-ican pain society, the American society of regional

anesthesia and pain medicine, and the American society of anesthesiol-ogists' committee on regional anesthesia, executive commi. JPain. 2016;17:131---57.4

9. 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.
10. Londhe S, Patwardhan M, Shah R, Oak M. Efficacy and safety of buprenorphine transdermal patch for immediate postoperative analgesia after total knee arthroplasty surgery. J Arthroplasty 2020;35:S178-81.
11. Kadapamannil D, Rajan S, Tosh P, Kumar L. Comparison of efficacy and safety of transdermal buprenorphine patch applied 48 versus 72 hours preoperatively in providing adequate postoperative analgesia following major abdominal surgeries. Indian J Pain 2018;32:46-50.)
12. Gupta H, Babu RJ. Transdermal delivery: product and patent update. *Recent Pat Drug Deliv Formul*. 2013;7(3):184-205.
13. Wirz S, Wittmann M, Schenk M, Schroeck A, Schaefer N, Mueller M, et al. Gastrointestinal symptoms under opioid therapy: a prospective comparison of oral sustained release-hydromorphone, transdermal fentanyl, and transdermal buprenorphine. *Eur J Pain.* 2009;13(7):737-43.)
14. Canneti A, Luzi M, Di Marco P, Cannata F, Pasqualitto F, Spinoglio A, et al. Safety and efficacy of transdermal buprenorphine and transdermal fentanyl in the treatment of neuropathic pain in AIDS patients. *Minerva Anestesiol.* 2013;79(8):871-83.
15. Miyazaki T, Hanaoka K, Namiki A, Ogawa S, Kitajima T, Hosokawa T, et al. Efficacy, safety and pharmacokinetic study of a novel fentanyl-containing matrix transdermal patch system in Japanese patients with cancer pain. *Clin Drug Investig*. 2008;28(5):313-25.
16. Vadivelu N, Anwar M. Buprenorphine in postoperative pain management. Anesthesiol Clin. 2010;28:601---9.
17. Macintyre PE, Huxtable CA. Buprenorphine for the management of acute pain. Anaesth Intensive Care. 2017;45:143---6.
18. Davis MP, Pasternak G, Behm B. Treating chronic pain: an overview of clinical studies centered on the Buprenorphine option. Drugs. 2018;78:1211---28.
19. Kress HG. Clinical update on the pharmacology, efficacy and safety of transdermal buprenorphine. Eur J Pain.2009;13:219---30.
20. Davis MP. Twelve reasons for considering buprenorphine as frontline analgesic in the management of pain. J Support Oncol.2012;10:209---19.
21. Kavanagh BP, Katz J, Sandler AN. Pain control after thoracic surgery. A review of current techniques. Anesthesiology 1994; 81:737–759.
22. Soto RG, Fu ES. Acute pain management for patients undergoing thoracotomy. Ann Thorac Surg 2003; 75:1349–1357.
23. Oliashirazi A, Wilson-Byrne T, Shuler FD, Parvizi J. Patient-controlled fentanyl iontophoretic transdermal system improved postoperative mobility compared to intravenous patient - controlled analgesia morphine: A pooled analysis of randomized, controlled trials. Pain Pract 2017;17:197-207
24. Machado FC, Neto GC, Paiva LO, Soares TC, Nakamura RK, Nascimento LF, *et al*. Uso da buprenorfina transdérmica na dor aguda pos - operatoria: Revisão sistemática [Transdermal buprenorphine for acute postoperative pain: A systematic review]. Rev Bras Anestesiol 2020;70:419-28.
25. Tassinari D, Sartori S, Tamburini E, Scarpi E, Raffaeli W, Tombesi P, *et al*. Adverse effects of transdermal opiates treating moderate - severe cancer pain in comparison to long - acting morphine: A meta - analysis and systematic review of the literature. J Palliat Med 2008;11:492-501.

Conflict of Interest: Nil Source of support: Nil