International Journal of Research in Medical Sciences
Angom CL et al. Int J Res Med Sci. 2024 Jul;12(7):2455-2460
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20241897

Original Research Article

Comparative study of transdermal buprenorphine and fentanyl patch for post-operative analgesia in abdominal surgery under general anaesthesia: a randomised single blinded study

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Received: 12 May 2024
Revised: 12 June 2024
Accepted: 17 June 2024

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ABSTRACT

Background: Postoperative pain is one of the main concerns for the patient undergoing any major surgery. Effective control of post-operative pain is a major challenge to the surgeon and the attending anaesthesiologist. In spite of recent developments in pain treatment, many patients still experienced moderate to severe pain after surgery.
Methods: The study groups divided into two, named group A and group B. The total sample size was 80, 40 patients in each group. Patients were allotted in two groups after block randomization viz: Group A (n=40)-patients received buprenorphine patch (10 µg/h) and patients in group B (n=40) received fentanyl patch of (25 µg/h).
Results: Difference in VAS scores among the two groups were found statistically significant from the end of surgery to 6 hours after surgery. However, from 12 hours after surgery, both the groups had comparable VAS scores. Among hemodynamic parameters, the heart rate and mean arterial pressure variation came out to be insignificant among both study groups. Group B showed more incidence of vomiting and constipation as compared to group A. There was no incidence of skin irritation, respiratory depression and urinary retention in both the groups.
Conclusions: The present study concluded that for elective abdominal surgeries under general anaesthesia, transdermal buprenorphine 10 mcg/hr and fentanyl 25 mcg/hr administered 12 hours prior to surgery are safe, reliable, maintaining haemodynamic stability with continuous effective post operative pain relief. Buprenorphine patch is more cost effective and PONV is more with fentanyl and hence, buprenorphine is better than fentanyl patch.

Keywords: Buprenorphine patch, Fentanyl patch, Transdermal drug delivery system

INTRODUCTION

Postoperative pain is one of the main concerns for the patient undergoing any major surgery. Effective control of post-operative pain is a major challenge to the surgeon and the attending anaesthesiologist. In spite of recent developments in pain treatment, many patients still experienced moderate to severe pain after surgery. It is estimated that severe postoperative pain is reported by 20-40% of patients undergoing surgical procedures, especially abdominal, thoracic, orthopaedic and pelvic surgeries.[1] Satisfactory perioperative analgesia improves the surgical outcome by reducing morbidity and organ dysfunction.[2] Pain can hamper the normal recovery process and extend the length of hospital stay, contribute towards patient dissatisfaction, cause a negative perception of hospital performance and increase the health care utilization costs. Multimodal analgesia is currently the best treatment for acute postoperative pain, however opioid therapy is still the main approach for the management of moderate to severe postoperative pain.[3]

Transdermal drug delivery systems (TDS) are simple, non-invasive and compliant method of delivery.[4] They are designed to provide sustained drug release for prolonged period resulting in constant plasma concentrations. TDS has been used in clinical practice as they overcome the pharmacokinetic problems of oral and parenteral routes.[5] Buprenorphine is a semisynthetic derivative of thebaine, 75-100 times more potent than morphine and causes less respiratory depression.[6] As a transdermal patch, buprenorphine is incorporated into an adhesive polymer matrix (acrylate vinyl acetate), which is continuously released into the systemic circulation over a period of seven days.[7] Fentanyl is a synthetic opioid, which is approximately 75 to 100-fold more potent compared to morphine.[8] Transdermal fentanyl patch provides analgesia in a discreet, convenient, non-invasive, and generally safe manner.[9]

So, based on the facts and findings of the previous studies, this study was conducted to compare the efficacy of the TDS of buprenorphine and fentanyl and associated adverse effects if any in patients undergoing elective abdominal surgery under general anaesthesia.

METHODS

After getting approval from the Research Ethics Board (REB), Regional Institute of Medical Sciences Hospital (RIMS), Imphal, Manipur. The total study duration of two years from January 2021 to October 2022. A randomized, single blinded study was carried out in 80 patients, aged 20 to 60 years, of either sex, ASA I and II who underwent elective abdominal surgeries under general anaesthesia. Sample size was calculated based on a previous study of Arshad et al and the registration of the study was done in the clinical trial registry of India CTRI/2021/08/035486.[10]

Patients were allotted in two groups after block randomization viz: Group A (n=40)-patients received Buprenorphine patch (10 µg/h) and patients in group B (n=40) received Fentanyl patch of (25 µg/h).

Inclusion criteria

Inclusion criteria includes patients undergoing elective abdominal surgeries under general anaesthesia, ASA (American Society of Anaesthesiology) category 1 and 2, and age group of 20 to 60 years of either sex.

Exclusion criteria

Exclusion criteria includes history of skin allergy, patients with history of allergic to study drugs and pregnant patients.

Pre-operative visit was done a day before surgery and a good rapport was established and eligible patients fulfilling the inclusion criteria were informed about the study and consent was sought. TDS was applied 12 hrs before surgery on hairless area of right upper arm of the patient, who was unaware of the TDS, the patient received.

On the day of surgery, in the pre-operative holding area, intravenous access was secured and patients were pre medicated with Inj. glycopyrrolate at the dose of 0.004 mg/kg intramuscularly, Inj. ondansetron 0.1 mg/kg intravenously and Inj. Fentanyl citrate 2 mcg/kg intravenously. Heart rate (HR), mean arterial pressure (MAP), systolic blood pressure (SBP), diastolic blood pressure (DBP) were monitored.

On arrival at the operation theatre baseline monitoring of HR, non-invasive blood pressure (NIBP), oxygen saturation (SPO_2) and electrocardiogram (ECG) were checked. After pre oxygenation for 3 minutes with face mask, induction was done with Inj. propofol (2 mg/kg) and after confirmation of bag and mask ventilation, succinylcholine (1.5 mg/kg) was given intravenously to facilitate endotracheal intubation. Correct endotracheal tube placement was confirmed with end tidal carbon dioxide ($EtCO_2$) and auscultation. Anaesthesia was maintained with sevoflurane 0.6-1% with a fresh gas flow of 5 l/min comprising of 67% nitrous oxide and 33% oxygen and adequate muscle relaxation with inj. vecuronium bromide 0.08 mg/kg body weight. Ventilation was adjusted to maintain end tidal CO2 between 35 to 40 mmHg.

The residual muscles relaxation was reversed using an inj. neostigmine and inj. glycopyrrolate and extubated and observed in the post anaesthesia care room. VAS scores assessed immediately at the end of the surgery, 1 hr, 2 hrs, 4 hrs, 6 hrs, 12 hrs and 2nd day and 3rd day of surgery and inj. dicofenac administered when VAS score was ≥4. Sedation level was assessed with Ramsay score. The findings and observations of the study were done using windows based statistical package for social sciences (SPSS) Version 21.0 (Armonk, NY: IBM Corp) and analysed.

RESULTS

Patients were allotted in two groups after block randomization viz: Group A (n=40) patients received Buprenorphine patch (10 µg/h) and patients in group B (n=40) received Fentanyl patch of (25 µg/h). Demographic characteristics, comparison of VAS (Visual Analogue Scale) between the study groups, comparison of RSS (Ramsay Sedation Scale) between the study groups and Adverse events mentioned in Table 1, Table 2, Table 3 and Table 4 respectively. Comparison of mean heart rate and mean arterial pressure between two groups shown in Figure 1 and Figure 2 respectively.

The age, weight, sex distribution and ASA grading between the two groups were found to be statistically insignificant ($p > 0.05$) (Table 1).

At all-time duration group A were found to have lower VAS scores than that of group B. Difference in VAS scores among the two groups were found statistically significant from the end of surgery to 6 hours after surgery. However, from 12 hours after surgery, both the groups had comparable VAS scores (Table 2).

Table 1: Demographic characteristics of the two groups.

Characteristics (Mean±SD)	Group A (buprenorphine)	Group B (fentanyl)	P value
Age (in years)	37.88±11.715	37.80±10.284	0.976
Weight (in kg)	59.75±7.167	60.17±10.045	0.828
Sex (M:F)	17:23	18:22	0.822
ASA (I:II)	35:5	36:4	0.723

Table 2: Comparison of VAS score between the two study groups.

VAS	Group A (buprenorphine) Mean±SD	Group B (fentanyl) Mean±SD	P value
At the end of the surgery	1.43±0.958	2.70±1.454	0.000
1 hr	1.08±0.917	1.98±1.000	0.000
2 hrs	0.60±0.709	1.10±1.057	0.015
4 hrs	0.28±0.599	0.80±1.018	0.006
6 hrs	0.10±0.379	0.70±1.114	0.002
12 hrs	0.73±1.086	1.43±2.171	0.072
2nd day	0.08±0.350	0.23±0.620	0.186
3rd day	0.08±0.350	0.20±0.608	0.263

Table 3: Comparison of RSS between the two study groups.

RSS	Group A (buprenorphine) Mean±SD	Group B (fentanyl) Mean±SD	P value
At the end of the surgery	2.35±0.48	2.58±0.59	0.067
1 hr	2.30±0.46	2.35±0.48	0.638
2 hrs	2.15±0.36	2.15±0.36	1.000
4 hrs	2.00±0.00	2.05±0.22	0.156
6 hrs	2.00±0.00	2.05±0.22	0.156
12 hrs	2.00±0.00	1.98±0.27	0.569
2nd day	2.00±0.00	2.00±0.00	1.000
3rd day	2.00±0.00	2.00±0.00	1.000

The Ramsay sedation score (RSS) in the two study groups were found to be statistically not significant (P value >0.05) (Table 3).

Table 4: Adverse events.

Complications	Group A		Group B		P value
	No.	%	No.	%	
Nausea	2	5	9	22.5	0.02
Vomiting	0	0	1	2.5	0.31
Constipation	2	5	3	7.5	0.64

The nausea, vomiting and constipation were the main side effects of the study drugs. The incidence of nausea was more in group B (22.5%; 9 patients) versus group A (5%; 2 patients) which was statistically significant (p= 0.02). There was only one incidence of vomiting in group B and none in group A. The incidence of constipation was higher in group B, 7.5% (3 patients) as compared to group A, 5% (2 patients), but was not statistically significant (p>0.05). There was no incidence of skin irritation, respiratory depression and urinary retention in both the groups (Table 4).

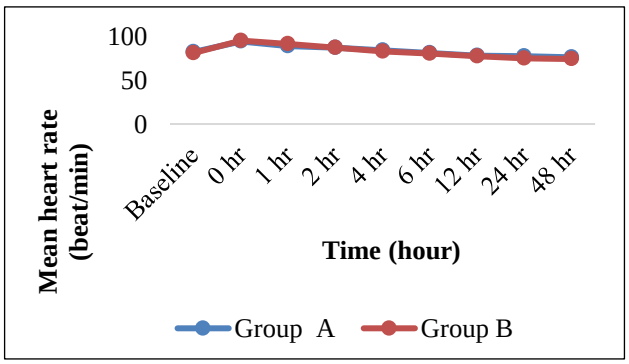

Figure 1: Comparison of mean heart rate (HR) in between the two groups.

The comparison of post operative HR among the two groups at the end of surgery, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours after surgery, 2nd day and 3rd day after surgery showed that the two groups was not statistically significant (P value >0.05) (Figure 1).

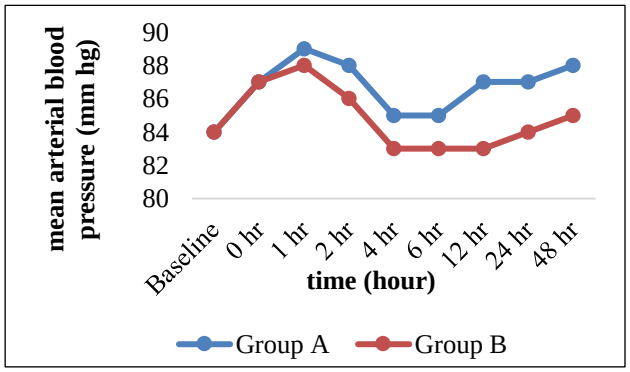

Figure 2: Comparison of mean arterial pressure (MAP) in between the two groups.

The post operative mean arterial pressure (MAP) among the two groups at the end of surgery at varied time intervals after surgery showed that it was not statistically significant (P value >0.05) (Figure 2).

DISCUSSION

Post-surgical pain is a complex response to trauma during surgery that stimulates the central nervous system. It raises the possibility of complications, cost of medical care and healing recovery.[11] Transdermal Drug Delivery System (TDS) provides safe, convenient and reliable method of drug delivery. It is a preferable alternative to oral and parenteral drug delivery method as it avoids painful skin punctures and multiple dosing. TDS has an advantage in having a high tendency for first-pass metabolism. These can be released in small doses with a sustained blood level.[10,11] It also decreases the incidence of breakthrough pain by providing sustained pain relief and thereby decreasing the requirement of rescue analgesics. Due to slow release of drug and avoiding sudden peaks in plasma drug levels, TDS also decreases the incidence of adverse effects associated with drugs. However, not all side effects are decreased as shown in some studies that the gastrointestinal side effects associated with oral and transdermal opioids are comparable.[10]

Fentanyl, a synthetic opioid with potent analgesic property has a low molecular weight and high lipid solubility. It is very suitable for TDS, delivering drug at constant rate viz: 25 to 100 micrograms/h and peaks at 12 to 40 hours.[10,12] Some of the adverse events of TDS of fentanyl are nausea, somnolence, vomiting, diarrhoea, constipation, pyrexia, insomnia and respiratory depression.[10]

Buprenorphine, semi-synthetic opioid analgesic. It is a partial agonist at the mu opioid receptor. The TDS provided post operative pain relief for one week.[10,13,14] It can be used with full mu-agonists without fear of antagonism. There is no ceiling effect or immunosuppressive activity with buprenorphine at therapeutic analgesic doses. The systemic adverse effects of buprenorphine are nausea, vomiting and constipation with locally are erythema and pruritis.

The dosage of each drug was decided after careful review of the various studies with different doses of buprenorphine and fentanyl by transdermal route and the effects of the different dose. It was observed that 10 µg/hour of transdermal buprenorphine and 25µg/hour of transdermal fentanyl had equianalgesic potency when compared to the standard drug morphine.[15]

There was no statistically significant difference found between two groups in regard to demographic profile and baseline characteristics as similar to the study done by Arshad et al and Jogdand et al.[10,16]

The comparison of the postoperative VAS scores was done immediately at the end of the surgery, 1hr, 2hr, 4hrs, 6hr, 12hr, 2nd day and 3rd after surgery and at all-time duration group A were found to have lower VAS scores than that of group B. Difference in VAS scores among the two group were found statistically significant from the end of surgery to 6 hours after surgery (p=0.002). However, from 12 hours after surgery, both the groups had comparable VAS scores. In this study, the result of VAS score suggested that both the patches were effective in controlling postoperative pain, but buprenorphine was better in this regard. Fentanyl patch had analgesic duration of action of 3 days while buprenorphine patch had duration of action of 7 days. So, buprenorphine provided longer pain relief compared to fentanyl, but the latter is a more effective analgesic. In Group A, 2 patients and in Group B,12 patients required single dose of rescue analgesic. Further, this finding resolved that buprenorphine patch is better analgesic than fentanyl patch which is comparable with the study done by Khandelwal et al.[17]

Arshad et al reported that fentanyl is better in controlling postoperative pain than buprenorphine, in contrast, it has been observed that in present study buprenorphine is superior than fentanyl, it may be because here in the present study the transdermal patch is applied 12 hours before surgery, rather than 6 hours as in Arshad et al study.[10] In a study conducted by Kumar et al and Niyogi et al they found that the peak effect of buprenorphine patch is achieved at 12-24 hours, so in this study the transdermal patch was applied 12 hours before surgery in order to achieved the desired drug concentration in the perioperative period.[11,18]

Comparison of the RSS between the two groups showed that there was no statistically significant change or drop

in RSS. All patients in both groups were calm, comfortable and easily arousable throughout the study and none of them showed excessive sedation or respiratory depression which is comparable with the study done by Shetty et al and Jogdand et al.[15,16]

The comparison of the heart rate and MAP showed no statistically significant difference between the two groups A & B. This shows that transdermal patches as such have no significant impact on blood pressure.

Nausea, vomiting and constipation were the main side effects of the study drugs. The incidence of nausea was more in group B (22.5%; 9 patients) versus group A (5%; 2 patients) which was statistically significant (p= 0.02). There was only one incidence of vomiting in group B and none in group A. The incidence of constipation was higher in group B, 7.5% (3 patients) as compared to group A, 5% (2 patients), but was not statistically significant (p>0.05). Besides opioid, many other factors may lead to nausea and vomiting such as female gender and abdominal surgery. Thus, the genesis of nausea was multifactorial.[10]

The present study is comparable to the study conducted by Shetty et al, Khandelwal et al and Wolff et al where they found that there were fewer side effects in patients who received TDS buprenorphine than those who received fentanyl patch.[15,17,19] The present study has comparable findings to that of a study conducted by Arshad et al who found that patients on fentanyl had a higher incidence of nausea and vomiting and there was no severe respiratory depression.[10]

This study has few limitations. Small sample size of the present study limits to come to a definitive conclusion. Ages >60 years were not included in the study and hence the effect of transdermal opioids in the elderly population was not studied. Plasma levels of the drug were not measured.

CONCLUSION

The present study concluded that for elective abdominal surgeries under general anaesthesia, transdermal buprenorphine 10mcg/hr and fentanyl 25mcg/hr administered 12 hours prior to surgery are safe, reliable, maintaining haemodynamic stability with continuous effective post operative pain relief. Buprenorphine patch is more cost effective and PONV is more with fentanyl and hence, buprenorphine is better than fentanyl patch.

ACKNOWLEDGEMENTS

Authors would like to thank the Department of Anaesthesiology, Regional institute of medical sciences, Imphal, Manipur, India. Authors would also like to thank the Junior Residents for helping in data collection, and to the HOD and other Senior Residents for helping in data compiling. Authors would like to thank the patients who had participated in this study.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee of RIMS, Imphal, Manipur

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Cite this article as: Angom CL, Singh KM, Roy LS, Kobing S, Sudarshan A, Thangaraj G. Comparative study of transdermal buprenorphine and fentanyl patch for post-operative analgesia in abdominal surgery under general anaesthesia: a randomised single blinded study. Int J Res Med Sci 2024;12:2455-60.