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COMPARISON OF EFFICACY OF TRANSDERMAL FENTANYL PATCH WITH BUPRENORPHINE PATCH POST-OPERATIVE PAIN RELIEF IN ABDOMINAL SURGERIES.

Anaesthesiology

Dr Chadha Poorvi* PG Resident, Department Of Anaesthesiology, Critical Care And Pain Management, Jaipur-302022, MGMCH, Rajasthan.*Corresponding Author

Dr Verma Kalpana Assistant Professor, Department Of Anaesthesiology, Critical Care And Pain Management, Jaipur-302022, MGMCH, Rajasthan.

Dr Moin Khayyam Associate Professor, Department Of Anaesthesiology, Critical Care And Pain Management, Jaipur-302022, MGMCH, Rajasthan.

Dr Jethava Durga HOD and Professor, Department Of Anaesthesiology, Critical Care And Pain Management, Jaipur-302022, MGMCH, Rajasthan.

ABSTRACT

Introduction: A transdermal drug delivery system (TDS) ensures steady and continuous drug delivery. It is usually applied preoperatively to provide optimal postoperative analgesia as the onset of action is delayed. Opioids are an important part of multimodal, perioperative analgesia, especially for pain. The transdermal route has several benefits over oral and parenteral administration. These include noninvasive dosing, better absorption, and lack of the first-pass metabolism with better patient compliance.

Materials and Methods: Sixty patients undergoing major abdominal surgery under GA were divided into two groups (n=30). Group F received 25 mcg/h fentanyl TDS; group B received buprenorphine 10 mcg/h TDS 12 hours before the surgery. Patients were followed for 50 hours post-surgery for postoperative pain relief and adverse effects.

Results: Baseline and demographic variables were comparable in both groups. The mean level of VAS was lower in group F as compared to group B at various intervals but statistically insignificant. The mean level of sedation score and hemodynamic variables were comparable in both groups. Rescue analgesia requirement was 16.7% (group B) versus 10% (group F). one patient had intractable nausea and vomiting with buprenorphine patch.

Conclusion: Transdermal Fentanyl and buprenorphine were safe and effective in controlling postoperative pain. Transdermal Fentanyl is better than buprenorphine in this respect.

KEYWORDS

INTRODUCTION:

Postoperative pain is a crucial for patients undergoing abdominal surgery. It is associated with adverse physiological and psychological effects hampering the functional recovery process.[1] The Incidence of persistent postsurgical pain is a worldwide problem leading to major negative effects on an individual's quality of life and also leading to increased hospital burden.

Various drugs and techniques have been used as a part of multimodal analgesia to relieve postoperative pain, with varying degrees of success and individual merits and demerits.[2] Preemptive analgesia, initiated before the surgical procedure, reduces post-operative pain by preventing intra-operative nociception and central sensitization, therefore, ensuring adequate postoperative pain relief, decreased consumption of opioids, and early mobilization. The transdermal drug delivery system (TDDS) a simple, non-invasive, and compliant method of delivery with the advantage of providing constant plasma concentrations unlike other routes of drug administration (3).

TDDS though used massively for chronic pain management, its utility in postoperative pain management is not yet fully investigated. Fentanyl and buprenorphine both drugs have low molecular weight, high potency, and lipid solubility thus making this ideal for delivery via the transdermal route. Hence, this study was conducted to compare the efficacy of transdermal fentanyl patch (TFP) with transdermal buprenorphine patch (TBP) for post-operative pain relief in major abdominal surgeries.

MATERIAL AND METHOD:

This prospective randomized double-blind comparative study was conducted in Mahatma Gandhi Medical College and Hospital after obtaining permission from the institutional ethics committee and informed consent from all the patients.

Sixty patients were randomly divided into two equal groups using a computer-generated list. Group B (buprenorphine group) received TBP (10ug/h), 12 hours before surgery. Group F (fentanyl group) received TFP (25mug/h), 12 hours before surgery. Drug patch was applied by staff nurse based on the generated list who received the patch in a sealed, opaque envelope. The patient, staff nurse, and investigator were unaware of the type of drug administered.

Inclusion criteria were, patients belonging to the ASA physical status class I/II, aged 20 to 60 years, and scheduled for elective abdominal surgeries under general anesthesia. Exclusion criteria were patients allergic to study drugs, having an intolerance to opioids, pregnant and breastfeeding females.

Drug patches were applied 12 hours before the proposed surgery on the hairless area of the chest, back, flank or upper arm to patients of both the groups after noting baseline hemodynamic parameters.

On the day of surgery, all the patients received general anesthesia following a standardized institutional protocol. Baseline vitals were recorded and the patients were premedicated with intravenous midazolam 1mg and fentanyl 2mcg/kg, induced with propofol 2mg/kg, muscle relaxation was achieved with vecuronium 0.1mg/kg. Anesthesia was maintained with oxygen, nitrous oxide (40:60 ratio), isoflurane, and intermittent boluses of vecuronium. Paracetamol 1gm after 2 hours of surgery was used to supplement analgesia. Patients were extubated after adequate signs of reversal of neuromuscular blockade with glycopyrrolate and neostigmine (0.01 mg/kg and 0.05 mg/kg respectively).

Postoperatively patients were monitored for 50 hours at various intervals for sedation and analgesia using the Ramsay sedation scale (1 = awake, 2 = drowsy, 3 = sleepy but arousable to verbal commands, 4 = sleepy but arousable to moderate stimulus, 5 = unconscious) and visual analogue score (0 being no pain and 10 being the worst pain) respectively. VAS score greater than 4 were treated with intravenous tramadol 1.5mg/kg to a maximum dose of 100 mg.

STATISTICAL ANALYSIS:

Data were subjected to statistical analysis using SPSS version 24. Differences between the two groups were determined using student t-test as well as chi-square test and the level of significance was set at $p < 0.05$.

RESULTS:

The age and gender distribution in both the groups were statistically insignificant (Table 1). Thus, both the groups were comparable in terms of age and gender.

Table 1: Age and gender distribution among the study subjects

Variables	Group B (n=30)	Group F (n=30)	p value
Age in years (Mean±SD)	38.58±8.03	39.01±9.17	0.72$^{\beta}$
Male, n(%)	24 (80)	22 (73.33)	0.81$^{\gamma}$
Female, n(%)	6 (20)	8 (26.67)	

β: t test, γ: Chi square test

The baseline characteristics of the patients are given in the (Table 2) The baseline systolic blood pressure, diastolic blood pressure, heart rate, and sedation score were statistically insignificant. (Table 2)

Table 2: Baseline characteristics among the study groups

Variables	Group B		Group F		t test	p value
	Mean	SD	Mean	SD		
SBP	134.91	4.03	137.32	5.74	1.38	0.19
DBP	83.37	4.48	86.39	3.87	1.61	0.12
Heart Rate	82.93	4.81	82.04	4.54	0.87	0.46
Sedation Score	1.64	0.58	1.52	0.49	0.73	0.60

[Table-3, 4] depicts the mean values of VAS and sedation score respectively post-extubation up to 50 hours in both groups. The mean VAS score was lower in group F as compared to group B at all time intervals. While the mean sedation score was lower in group B as compared to group F in the immediate post-operative period, comparable at first hour post-extubation and curtailed thereafter till 50 hours post-extubation in both the groups. However, the VAS score and sedation score remained statistically insignificant throughout the observation between the groups.

Table 3: Comparison of VAS score post-operatively

Follow-up (Post Extubation)	Group B		Group F		t test	p value
	Mean	SD	Mean	SD		
0.5 Hour	3.97	0.78	3.73	0.69	0.43	0.68
1 Hour	3.80	0.64	3.49	0.86	0.81	0.47
1.5 Hour	3.61	0.72	3.32	0.91	1.17	0.39
2Hour	3.12	0.93	2.87	0.77	1.48	0.32
8 Hour	2.69	1.02	2.54	0.83	0.89	0.43
14 Hour	2.63	0.91	2.48	0.74	1.18	0.32
20 Hour	2.62	0.82	2.43	0.42	1.79	0.19
26 Hour	2.60	0.62	2.34	0.67	1.92	0.16
34 Hour	2.60	0.70	2.31	0.58	2.41	0.09
42 Hour	2.51	0.56	2.28	0.49	2.32	0.14
50 Hour	2.48	0.67	2.19	0.81	2.38	0.11

Table 4: Comparison of sedation score post-operatively

Follow-up (Post Extubation)	Group B		Group F		t test	p value
	Mean	SD	Mean	SD		
0.5 Hour	3.35	0.69	3.42	0.53	0.5	0.65
1 Hour	3.18	0.55	3.18	0.7	0.88	0.44
1.5 Hour	2.99	0.63	2.76	0.75	1.24	0.36
2Hour	2.5	0.84	2.4	0.61	1.55	0.29
8 Hour	2.11	0.67	2.07	0.93	0.96	0.4
14 Hour	2.01	0.82	1.96	0.58	1.25	0.29
20 Hour	2	0.73	1.78	0.26	1.86	0.16
26 Hour	1.98	0.53	1.71	0.51	1.99	0.13
34 Hour	1.98	0.61	1.56	0.42	2.48	0.06
42 Hour	1.89	0.47	1.49	0.33	2.39	0.11
50 Hour	1.86	0.58	1.45	0.65	2.42	0.08

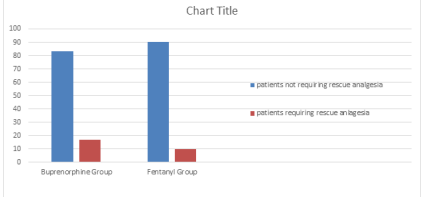

Figure 1: Percentage of patients requiring and not requiring rescue analgesics.

Figure 1 depicts the percentage of patients requiring rescue analgesics**.** In group B, 16.6% of patients required rescue analgesia as compared to 10% of patients in group F. Although this difference in rescue analgesic requirement was not statistically significant.

The average time for rescue analgesia requirement in group B was 3 hours as compared to 5 hours in group F. The average dose of supplemental analgesic administered in group B was 1.6 doses of tramadol as compared to 1 dose of tramadol in group F.

As per the incidence of adverse effects, one patient of group B experienced severe nausea and vomiting post-surgery and was treated with injection ondansetron 4mg and subsequent removal of the patch.

DISCUSSION

TDDS are in the form of adhesive patches of various sizes 5-20 cm2 which deliver the contained drug at a persistent rate into the circulation via the stratum corneum. Highly lipid-soluble drugs can be applied over the skin for slow and prolonged, sustained absorption. TDDS provides an easy, non-invasive and compliant method of sustained drug delivery. (3) Their minimal interference with daily activities makes them an effective alternative to parenteral and oral drug delivery methods for postoperative analgesia.

TDDS allows continuous drug delivery to reach the sustained plasma concentrations thereby decreasing the incidence of breakthrough pain by providing the analgesia before the surgery. It by-passes the first-pass metabolism by the liver, increasing bioavailability and limiting variation in plasma concentration thereby enables the use of lower drug doses with curtailed adverse effects (6).

Buprenorphine is a semi-synthetic opioid analgesic. It acts on mu-opioid receptors as a partial agonist. TDS preparation provides pain relief for a week [5]. Buprenorphine in therapeutic dose range analgesia does not show ceiling effect. It can be used as full mu-agonists unaccompanied with the fear of antagonism. There is no immunosuppressive activity with buprenorphine at therapeutic analgesic doses unlike morphine and fentanyl. [6]. The new buprenorphine TDS is an important modality for patients with chronic pain [7,8]. The buprenorphine patch is available in five strengths: 5, 7.5, 10, 15, and 20 µg/hr. Each 10 ug/hr BUVALOR patch has 10mg of buprenorphine in a 12.5 cm^2 surface area releasing a nominal 10 micrograms of buprenorphine per hour for 7 days with peak plasma concentration reaching after 12-24 hours after application which can be used for 7days. More than one patch can be applied depending on the quality of pain relief, but the total dosage should not exceed 20 µg /hr. (7,8)

Fentanyl is a synthetic opioid with powerful analgesic activity. Its low molecular weight and high lipid solubility make it is perfect for delivery via the transdermal therapeutic system (TTS). This route provides the drug at a constant delivery ranging from 25 to 100 micrograms/hour [1]. The gradual onset and huge variability between patient-to-patient of TTS fentanyl, with limited duration of analgesia and a high incidence of respiratory depression made anesthesiologists resistant to use it as acute postoperative analgesic. TTS fentanyl causes fewer gastrointestinal adverse events when compared with morphine [3]. Fentanyl patches are available in strengths of 12, 25, 50, 75, and 100 µg/hour, acquiring the peak concentrations in 6-12 hours after application. (4)

Canneti et al in 2013 conducted a study in AIDS patients for neuropathic pain and concluded the high efficacy, tolerability and patient compliance of transdermal buprenorphine and fentanyl make valid therapeutic options [4]

In our study, we have compared the effect of two opioids via the transdermal route in postsurgical patients for upto 50 hours to determine their analgesic efficacy. The demographic and hemodynamic variables in both groups were comparable and there was no clinically significant variation from the baseline values.

VAS score was relatively higher in group B as compared in group F in the first 8 hours postoperatively but the difference was statistically insignificant. However, the average trend of VAS remained consistent throughout 50 hours post-operatively in both the groups, though group F had better control of pain compared to group B.

Zia Arshad et al also compared transdermal buprenorphine and

fentanyl for postoperative pain relief, observed that 5 patients in the buprenorphine group required rescue analgesia while none of the patients in the fentanyl group needed postoperative analgesia, the observation is similar to our results.

In our study, buprenorphine group five patients required rescue analgesia, three required two doses of rescue analgesia while two required only a single dose of rescue analgesia and in the fentanyl group, three patients required only a single dose of rescue analgesia 50 hours postoperatively.

Saikat Niyogi et al applied transdermal buprenorphine patch and placebo group patch 24 hours before the surgery on 70 adult patients, concluded that there was a significant decrease in the total rescue analgesic requirement.

The dose of rescue analgesia requirement was comparatively higher with BTP suggesting that the peak effect of the drug is 20-24 hrs. BTP has manufacturer-recommended a duration of action of 7 days while FTP has duration of action of 72 hours. Therefore, BTP provides longer action as compared to FTP but the latter is a more effective analgesic.

Setti et al used 17.5, 35, and 52.5 µg/h strength TDB patches in patients undergoing gynecologic surgeries. They found that the consumption of rescue analgesia was inversely correlated to the TDB dosage but was directly proportional to patient satisfaction. Similarly, in our study, the first rescue analgesic requirement was delayed and comparatively less in the TDF Group as compared to the TDB Group. Post-operative frequency and total doses of tramadol administration were higher in the TDB group than the TDF group though the difference was not statistically similar.

Although sedation scores were higher in group B as compared to group F on Statistical analysis at most time intervals, average score remained below 3 on a majority of the occasions but was statistically similar.

All patients of either group were calm, comfortable, and arousable throughout the study without respiratory depression. On comparing with the baseline sedation scores, we found that sedation scores escalated more in group B than group A. So, we conclude that BTP provides more sedation than FTP but this difference was statistically not significant.

The Study by Sunil Rajan et al compared transdermal and epidural buprenorphine and applied the patch 24 hr preoperatively and concluded that sedation scores were comparatively higher with patch group.

Comparison of adverse effect profile revealed the single patient experience of nausea and vomiting with buprenorphine patch. The fentanyl patch group on the contrary did not report any adverse event which was significantly lower than observed in other studies [4,6, 9]. Besides opioids, many other factors may lead to nausea and vomiting such as female sex and abdominal surgery. Thus, the genesis of nausea was multifactorial. Hence the incomparable discreet results.

Miyazaki et al did a study on chronic cancer pain patients and found hemodynamic variation in terms of bradycardia with fentanyl TDS while in our study no such adverse effect was seen. (9)

BTP was also shown to be an effective analgesic against chronic, severe pain in this study population. Patients treated with this new formulation of buprenorphine showed an improved duration of sleep and reduced need for additional oral analgesics [11]. Our study demonstrated its usefulness in postoperative pain also.

FTP has not been used extensively studied the postsurgical patients due to fear of respiratory depression, but used in cancer and chronic pain [12,13]. In our study, none of the patient experienced serious side effects. Thus, according to our study use of fentanyl TDS in suitable patients is as safe, effective, and compliant as other opioids.

Considering the cost of the transdermal patches, the fentanyl patch is available at INR 500 while the buprenorphine patch is available at INR 1290 (Buvlor ™ 10 mcg). Fentanyl TDS acts for 3 days while buprenorphine TDS works for a week. So, buprenorphine TDS is more cost effective than fentanyl TDS.

Limitations:

One of the major limitations of our study was that we used a visual analogue rating score for the assessment of the efficacy of analgesia, which had subjective variations in pain perception.

CONCLUSION:

Thus, we can conclude that buprenorphine and fentanyl patches both are very effective in controlling post-surgical pain and fentanyl is better in this regard. Because fentanyl TDS has better analgesia with minimal sedation. However, considering cost-effectiveness, buprenorphine TDS is better as it is cheaper and can be used for 7 days. So, we recommend both can be used for analgesia in suitable patients.

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