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COMPARISON BETWEEN TRANSDERMAL BUPRENORPHINE AND TRANSDERMAL FENTANYL FOR POSTOPERATIVE PAIN RELIEF AFTER EMERGENCY LAPAROTOMY UNDER GENERAL ANAESTHESIA

Anesthesiology

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ABSTRACT

Introduction-: Opioid are one of the most commonly used analgesics for post operative pain and their transdermal patches provide sustained blood levels of the drug for sufficient period. Transdermal drug delivery system (TDDS) is one of the systems lying under the category of controlled drug delivery, in which the aim is to deliver the drug through the skin in a predetermined and controlled rate. It has various advantages, like prolonged therapeutic effect, reduced side-effects, improved bioavailability, better patient compliance and easy termination of drug therapy. We compared two available opioid transdermal patch for postoperative pain relief after emergency laprotomy under general anaesthesia.

Material and Methods-: It was a prospective randomized double blind comparative study involving 60 adult patients undergoing major abdominal surgery under general anaesthesia (GA). After getting approval from the institutional ethical committee, patients were divided into 2 groups randomly. Each group had 30 patients (n=30). Group A: This group received Buprenorphine patch (10 µg/h), on hairless area of upper arm. Group B: This group received Fentanyl patch of (25 µg/h), on hair less area of upper arm.

All the quantitative data (H.R., S.B.P., D.B.P., R.R., SpO2, VAS Score , Ramsay Sedation Score) were summarized in the form of mean ± SD. The difference between mean value of both groups was analyzed using Student't' test.

Results-: The systolic blood pressure (SBP), diastolic blood pressure (DBP), visual analogue scale (VAS) and Ramsay sedation score (RSS) were insignificantly different at Day 1. The mean level of VAS was significantly lower in group B as compared to group A at Day 1, 2 and 3. The incidence of nausea, urinary retention and constipation were comparable in both groups (p-value= 1.0000). The total no. of adverse events in both groups did not differ significantly (p-value= 1.0000). None of the patient in both group experienced skin irritation and respiratory depression. in group A out of 30 patients, 5 patients received one dose of rescue analgesic, 2 patients received 2 doses of rescue analgesic and 1 patients received 3 doses of rescue analgesic in 72 hour while in group B 8 patients received One dose of rescue analgesic in 72 hour after Surgery. Total doses of rescue analgesic Inj. Diclofenac 75mg in group A patients was 13 and in group B patients was 8, This difference in rescue analgesic requirement is not quiet statistically significant (p-value 0.0522).

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

KEYWORDS

INTRODUCTION

Pain is defined by the International Association for the Study of Pain (IASP,2012) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in term of such damage"[1].

Postoperative pain is one of the main concerns for the patient undergoing major surgery. It is a challenge to the treating surgeon and attending anaesthesiologist as there are many adverse physiological and psychological effects associated with pain, which can hamper the normal recovery process. Various techniques and drugs have been used for this purpose with variable success. Every technique and drugs has its own advantages and disadvantages.

Transdermal drug delivery system (TDDS) is one of the systems lying under the category of controlled drug delivery, in which the aim is to deliver the drug through the skin in a predetermined and controlled rate. It has various advantages, like prolonged therapeutic effect, reduced side-effects, improved bioavailability, better patient compliance and easy termination of drug therapy. According to the duration of therapy, various drugs are commercially available in the form of transdermal patch. They are available for analgesics like opioid (fentanyl and buprenorphine) and NSAIDS (diclofenac), antihypertensive like NTG, hormones (estrogen, testo sterone), anticholinergics (scopolamine), clonidine, rivastigmine, MAOI selegiline, methylphenidate, cynocobalamine, nicotine etc [1].

Opioid are one of the most commonly used analgesics for post operative pain and their transdermal patches provide sustained blood levels of the drug for sufficient period. We compared two available opioid transdermal patch for postoperative pain relief after emergency laprotomy under general anaesthesia".

AIMS AND OBJECTIVES

This study was designed primarily for "Comparison between Transdermal Buprenorphine and Transdermal Fentanyl for Postoperative Pain Relief after emergency laparotomy under general anaesthesia". Aim of this study was to compare the following parameters:

1. analgesic efficacy.
2. Sedation .
3. Effect on H.R. , B.P. and respiration.
4. Adverse effect to study drug.

MATERIAL AND METHODS

It was a prospective randomized double blind comparative study involving 60 adult patients undergoing major abdominal surgery under general anaesthesia (GA). Patients of age 20-50 years, undergoing emergency laprotomy under general anaesthesia.

Exclusion Criteria:- Patients allergic to study drugs, having intolerance to opioid, pregnant and breastfeeding females, having impaired pulmonary function H/o habituation/ addiction to any narcotic and were excluded from the study.

After getting approval from the institutional ethical committee, patients were divided into 2 groups randomly. Each group had 30 patients (n=30).

Group A: This group received Buprenorphine patch (10 µg/h), on hairless area of upper arm.

Group B: This group received Fentanyl patch of (25 µg/h), on hair less area of upper arm.

Complete medical history and physical examination including vital signs and airway assessment for all patients was done. Study Drug patches (Buprenorphine -group A, Fentanyl- group B) was applied to patients 6 hours before proposed surgery after noting baseline haemodynamic parameters.

At the time of surgery patients were premedicated with inj. Midazolam 1 mg IV, inj. Fentanyl 2 mcg/kg IV and inj ondensetron 4 mg IV. Patients were induced with propofol 2 mg/kg and intubated with vecuronium 0.1 mg/kg. Anaesthesia was maintained with Isoflurane 1-2% in oxygen and muscle relaxation with non depolarizing muscle relaxant vecuronium.

Patients were extubated after reversing neuromuscular blockade with glycopyrrolate and neostigmine (0.01 mg/kg and 0.05 mg/kg respectively).

Sedation and analgesia was assessed using Ramsay sedation scale and visual analogue score respectively for the next 3 days 12 hourly. Haemodynamic parameters and any adverse effects were also noted. Inj diclofenac (75 mg IV) was used as a rescue analgesic in patient complaining of inadequate pain relief.

Statistical Analysis-

All the quantitative data (H.R., S.B.P., D.B.P., R.R., SpO2, VAS Score , Ramsay Sedation Score) were summarized in the form of mean ± SD. The difference between mean value of both groups was analyzed using Student't' test. Requirement of Rescue analgesic was summarized in the form of proportions. The differences between proportions was analyzed using Chi square test. A P value <0.05 was considered as significant (S) .

RESULTS

The baseline characteristics of the patients are given in the [Table/ Fig-1]. The age of both the groups was almost similar and male/ female ratio was also similar. Thus, both the groups were comparable in terms of age and sex.

The systolic blood pressure (SBP), diastolic blood pressure (DBP), visual analogue scale (VAS) and Ramsay sedation score (RSS) were insignificantly different at Day 1.

Table 1-Baseline characteristics of the patients

Characteristics	Group A (N=30)	Group B (N=30)	p-value
Age in years	37.1±11	38.8±8.98	0.60
Male gender, no. (%)	23 (74.3)	24 (80)	0.52
SBP	135.12+4.68	133.11+3.74	0.08
DBP	81.55+3.65	82.69+3.49	0.21
Heart rate	80.65+4.10	80.72+4.35	0.92
VAS	4.48+0.40	4.49+0.62	0.95
Sedation score	1.58+0.48	1.42+0.48	0.20

[Table-2] depicts the mean values of VAS from Day 1 to Day 3 in both groups. The mean level of VAS was significantly lower in group B as compared to group A at Day 1, 2 and 3.

Table 2- Change in VAS from Day 1 to Day 3

Follow up day	Group A(n=30)	Group B(n=30)	P-Value
Day 1	4.45+0.36	2.46+0.62	<0.0001
Day 2	4.33+0.33	3.22+0.59	<0.0001
Day 3	4.36+0.55	3.89+0.52	0.002

[Table-3] depicts the mean values of sedation score from Day 1 to Day 3 in both groups. The mean level of sedation score was significantly lower in Group B than Group A.

Table 3-Mean values of sedation score

Follow up day	Group A(N=30)	Group B(n=30)	p-value
Day 1	1.83+0.45	1.38+0.44	0.0003
Day 2	1.79+0.32	1.44+0.45	0.0022
Day 3	1.86+0.30	1.42+0.21	<0.0001

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

The incidence of adverse effects is shown in [Table-4]. The incidence of nausea, urinary retention and constipation were comparable in both groups (p-value= 1.0000). The total no. of adverse events in both groups did not differ significantly (p-value= 1.0000). None of the patient in both group experienced skin irritation and respiratory depression.

Table 4: ADVERSE EFFECT

ADVERSE EFFECT	Group A		Group B	
	No of patients (n=30)	percentage	No of patient (n=30)	percentage
Nausea	6	20.00%	7	23.33%
Vomiting	7	23.33%	9	30.00%
Constipation	3	10.00%	3	10.00%
Respiratory Depression	0	0%	0	0%
Euphoria/ Dysphoria	2	6.66%	1	3.33%

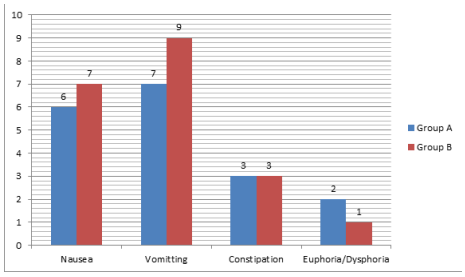


Table 5- Total number of rescue analgesic required in 72 hours

No of rescue analgesic in 72 hr	Group A		Group B	
	No of patients	Percentage	No of patients	Percentage
0	22	73.33%	22	73.33%
1	5	16.66%	8	26.66%
2	2	6.66%	0	0
3	1	3.33%	0	0
Stastical Significance	P value > 0.05(NS)Not Significant			

As shown in table no. 5, in group A out of 30 patients, 5 patients received one dose of rescue analgesic, 2 patients received 2 doses of rescue analgesic and 1 patients received 3 doses of rescue analgesic in 72 hour while in group B 8 patients received One dose of rescue analgesic in 72 hour after Surgery. Total doses of rescue analgesic Inj. Diclofenac 75mg in group A patients was 13 and in group B patients was 8, This difference in rescue analgesic requirement is not quiet statistically significant (p-value 0.0522).

DISCUSSION

Transdermal drug delivery system (TDS) provides safe, convenient and sustained method of drug delivery. It is a preferable alternative to parentral and oral drug delivery methods as it avoids painful skin punctures and multiple dosing. TDS allows sustained delivery of drug to plasma without first pass metabolism. Many drugs which have a high first pass metabolism are given through TDS such as Buprenorphine, Clonidine, Estradiol, Fentanyl, Granisetron, Lidocaine, Methylphenidate, Nicotine, Nitroglycerin, Oxybutynin, Rivastigmine, Rotigotine, Scopolamine, Selegiline, Testosterone, Influenza virus vaccine, etc [1]. TDS allow continuous drug delivery and sustained plasma levels thereby avoiding peaks and turphs in the plasma levels of the drug. 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 [2].

Fentanyl is a synthetic opioid with potent analgesic activity. Fentanyl has low molecular weight and high lipid solubility therefore it is suitable for delivery via the transdermal therapeutic system (TTS). These systems provide drug at constant rate ranging from 25 to 100 micrograms/h [1]. However, risk of respiratory depression makes fentanyl TTS relatively contraindicated in this setting. At the start of fentanyl TTS treatment, drug first accumulates within skin tissue and then gradually released in systemic circulation which results in a significant delay (17 to 48 hours) before maximum plasma concentration is achieved. The duration of onset of analgesia is noted to be 1.2 to 40 hours and peak effect reaches to 1.2 to 40 hours. Analgesia lasts upto three days [3].

Slow onset and large patient to patient variability of TTS fentanyl,

along with the relatively short duration of analgesia and a high incidence of respiratory depression made anaesthesiologist reluctant to use it for acute postoperative pain. In comparison with oral morphine, TTS fentanyl causes fewer gastrointestinal adverse events [3].

Buprenorphine is a semi-synthetic opioid analgesic. It is a partial agonist at the mu opioid receptor. TDS provides pain relief for one week [5]. Ceiling effect to analgesia was not seen within the therapeutic dose range. Buprenorphine can be used with full mu-agonists without fear of antagonism. Buprenorphine has no immunosuppressant activity at analgesic concentration as seen with fentanyl and morphine. Unlike morphine and fentanyl, there is no immunosuppressive activity with buprenorphine at therapeutic analgesic doses [6]. Systemic adverse effects included nausea, vomiting and constipation. Local adverse events are erythema and pruritis. The new buprenorphine TDS appears to be an important new modality for administering analgesia in patients with non-acute pain [7,8].

In our study, we compared the two opioid TDS in postsurgical patients for 3 days to determine their safety and efficacy, as from the above discussion we can see that fentanyl TDS is considered relatively contraindicated in postsurgical patients. The haemodynamic variables in both groups were comparable and did not show any clinically significant deviation from the baseline values. We did not found any adverse haemodynamic events in our study in either group [9].

The VAS scores, which were used to quantify the pain, were significantly reduced from day 1 to 3 in group B as compared to group A. On comparing with the baseline values, we found that the VAS was not significantly reduced in group A and it seems that buprenorphine TDS is not effective in decreasing pain but we must keep in mind that buprenorphine TDS has not allowed VAS to increase after surgery which normally happens. Thus we can see that buprenorphine TDS is effective in attenuating postsurgical pain. While in group B, VAS is significantly decreased from the baseline and also it is significantly lower than group A from day 1 to 3, suggesting that fentanyl TDS is more effective in controlling postsurgical pain. Therefore, we can conclude that both TDS were effective in controlling postoperative pain. However, fentanyl was better in this regard. Five patients in group A required single dose of rescue analgesic within first 4 hours after surgery and no further rescue analgesic was required. While in group B, no rescue analgesic was required. This further consolidates our conclusion that fentanyl TDS is better analgesic than buprenorphine TDS. Buprenorphine TDS has manufacturer recommended duration of action of 7 days while fentanyl TDS has duration of action of 72 hours. Therefore, buprenorphine TDS provides longer pain relief as compared to fentanyl TDS but the latter is more effective analgesic.

Although sedation scores were significantly higher in group A as compared to group B on Statistical analysis but they were below 2 throughout the treatment period. All patients were calm, comfortable and easily aruosable throughout the study and none of the patient showed excessive sedation or respiratory depression. On comparing with the baseline sedation scores, we found that sedation scores were not changed in group B as compared to baseline but they are higher in group A. So, we conclude that buprenorphine TDS provides more sedation than fentanyl TDS but this difference is not clinically significant.

Buprenorphine TDS 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 improved duration of sleep and reduced need for additional oral analgesics [13]. Our study proved its usefulness in postoperative pain also.

Fentanyl TDS is not extensively studied in postsurgical patient due to fear of respiratory depression. However, it has been used in cancer and chronic pain [14,15]. In our study, we showed that it is not as serious problem as thought. The use of fentanyl TDS in suitable patient is as safe and effective as other opioid.

Considering the cost of the transdermal patches, fentanyl patch is available at INR 1450 (Duragesic ™ 25 mcg) while buprenorphine patch is available at INR 890 (Buvlor ™ 10 mcg). Fentanyl TDS works for 3 days while buprenorphine TDS works for 5 days. So, buprenorphine TDS is cheaper than fentanyl TDS.

limitations

The limitations of our study includes comparison in lower abdominal surgery only, use of subjective VAS scale for analgesia, follow up only for 3 days and not measuring plasma levels of drug.

CONCLUSION

Thus, we can conclude that both buprenorphine and fentanyl TDS were effective in controlling postsurgical pain and fentanyl is better in this regard. Because fentanyl TDS has better analgesia with less sedation. However, on considering cost effectiveness, buprenorphine TDS is better as it is cheaper and can be used for 5 days. So, we recommend both TDS for postoperative analgesia. Buprenorphine is more cost effective and of longer duration and should be preferred. However, if greater analgesia is required then fentanyl TDS is better.

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