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Use of Transdermal Buprinorphine Patch or Transdermal Fentanyl Patch for Post Operative Pain Relief in Lower Limb Surgeries –A Comparative Study

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A B S T R A C T

Introduction*:** Opioid is commonly used analgesics for postoperative pain. Various modes of delivering drug are present but transdermal drug delivery system is safe, sustained, non-invasive, better absorption and lack of first-pass metabolism. Bolus dosing results in toxic plasma levels and inadequate duration of analgesia.Methods*:** It is prospective, randomized, double blind comparative study, conducted after obtaining approval from institutional ethics committee and written informed consent from patients. Patients of age 18-60yrs, undergoing lower limb surgeries under Spinal Anesthesia (SA) with ASA-1 status were included in study. Patients with drug allergy or intolerance to opioids were excluded. Patients' were randomly assigned into 2groups of 45 each, Group B received Buprenorphine 10mcg/h TDS and group F received 25mcg/h Fentanyl TDS, 6 hours prior to surgery. Patients were followed for three days for postoperative pain relief and adverse effects. Statistics used was Student t-test, Fischer-exact test and Chi-square test.***Results*:** Baseline and demographic variables are comparable in both groups. Mean level of VAS was significantly lower in group Fentanyl as compared to group Buprenorphine. Mean level of sedation score was significantly lower in Group Fentanyl than Group Buprenorphine. Haemodynamic variables in both groups (SBP, DBP and HR) showed no significant difference. 6 out of 45(13.3%) patients in group Buprenorphine required single dose of rescue analgesic while 0 patients in group fentanyl and requirement is statistically significant (p-value=0.026). 20% patient in Group Fentanyl and 17.8%patients in Group Buprenorphine experienced some adverse effects.***Conclusion*:** Fentanyl and buprenorphine TDS were effective and safe in controlling postoperative pain but Fentanyl is better than buprenorphine in this respect.

Keywords: Fentanyl; Buprenorphine; Postoperative pain.

INTRODUCTION

Patients undergoing lower limb surgeries are known to experience severe degrees of pain in the post-operative period. Persistent, intense pain activates secondary mechanisms both at the periphery and within the central nervous system that cause allodynia, hyperalgesia and hyperapathia that can diminish normal functioning and may lead to chronic pain [1]. Adequate pain management is a challenge to the pain physician as there are many adverse psychological and physiological effects associated with it [2]. Hence, effective analgesia in this population is essential to accelerate functional recovery and enable patients to return to their normal activity more quickly after rehabilitation. Although many methods are available for post-operative pain management, newer approaches are constantly being investigated. Usually, post-operative analgesia includes NSAIDs or opioid drugs like morphine and fentanyl taken intravenously, intramuscularly or per-orally. Recent times have witnessed the introduction of a newer modality of therapy: transdermal patches containing opioids for pain relief. Although its use is more prevalent in treating patients experiencing severe

cancer pain, studies are now being conducted to popularize it for post-operative analgesia. Buprenorphine and fentanyl are two such opioid analgesics available as transdermal patches that are being used for their analgesic effects in the post-operative period. Buprenorphine is a non-selective mixed agonist–antagonist opioid receptor modulator, acting as a partial agonist of the μ receptor, an antagonist of the κ and the δ-receptors, δ-receptor. Its active metabolite norbuprenorphine, acts as a strong agonist at the δ-receptors [3]. It has physicochemical properties, including a low molecular weight and high analgesic potency that makes it an excellent compound for [2] transdermal drug delivery. The new technology of transdermal buprenorphine (TDB) is an advanced system that contains the active drug incorporated into a polymer matrix, which is at the same time the adhesive layer. The patch precisely controls the rate of drug delivery and produces stable plasma concentrations within 48 hours of the first application. Patch adhesion analysis shows the appropriateness of the seven-day application period [4, 5]. Fentanyl is a pure μ-opioid receptor agonist known for its analgesic and sedative effects. It bypasses the first pass metabolism in the liver and hence has high bioavailability. Moreover, owing to the high lipophilic action, it is an ideal agent for transdermal delivery and it achieves a large volume of distribution. The transdermal patch provides consistent diffusion of fentanyl over a 72-hour period [6]. The purpose of this study is to find out which transdermal opioid analgesic among the two is more efficacious in terms of postoperative analgesia and which one has a better side effect profile.

Aim of Study

To study the post operative analgesia and compare the effectiveness of transdermal buprenorphine and transdermal fentanyl for postoperative pain relief.

METHODOLOGY

Source of data:

It is a prospective, randomized single blind study in patients of age group 18-60 years and of American Society of Anesthesiologists (ASA) physical status I and physical status II posted for elective lower extremity surgery at Navodaya Medical College (NMC), Raichur, Karnataka.

Study site: Navodaya Medical College, Hospital and Research Centre, Raichur.

Study design: Prospective, randomized single blind study.

Sample size: 90 with each group having 45 patients

Inclusion criteria

1) Age – 18 to 60 years of either sex.
2) Patients belonging to ASA -Grade I and II
3) Patients undergoing elective lower limb surgeries

Exclusion criteria

1) Patients with history of drug abuse or alcohol abuse
2) Patients with known allergy to fentanyl and buprenorphine.
3) Patients on antidepressants, antipsychotics, anxiolytics and anticonvulsants.
4) Patients' refusal for the procedure.

Methodology:

We planned to conduct a prospective randomized single blind comparative study involving adult patients undergoing major lower limb surgery under spinal anaesthesia. Written and informed consent was taken from the patient, patients satisfying the inclusion and exclusion criteria were randomly allocated, using a computer-generated random number table and sealed envelope technique, to one of the following two groups of patients.

Group A: This group received Buprenorphine patch (10mcg/hr)

Group B: This group received Fentanyl patch of (25mcg/hr)

Drug patches were applied to patients 12 hours before proposed surgery in both groups after noting baseline hemodynamic parameter. Patients were premedicated with Antacids and Anxiolytics i.e., Tab Ranitidine 150 mg po and Tab Alprazolam 0.5mg PO HS under strict aseptic precautions 25 g Quincke's Babcock spinal needle was inserted in L3-L4 and 0.5% (H) bupivacaine was injected. Adequate block was achieved. Analgesia was assessed using visual analogue score, Ramsay Sedation Score (RSS) 40 and hemodynamic parameters respectively for next 3 days 12 hourly. Hemodynamic parameters and any adverse effects were also noted if any. Injection diclofenac (75mg IV) was used as a rescue analgesic in patient complaining of inadequate pain relief.

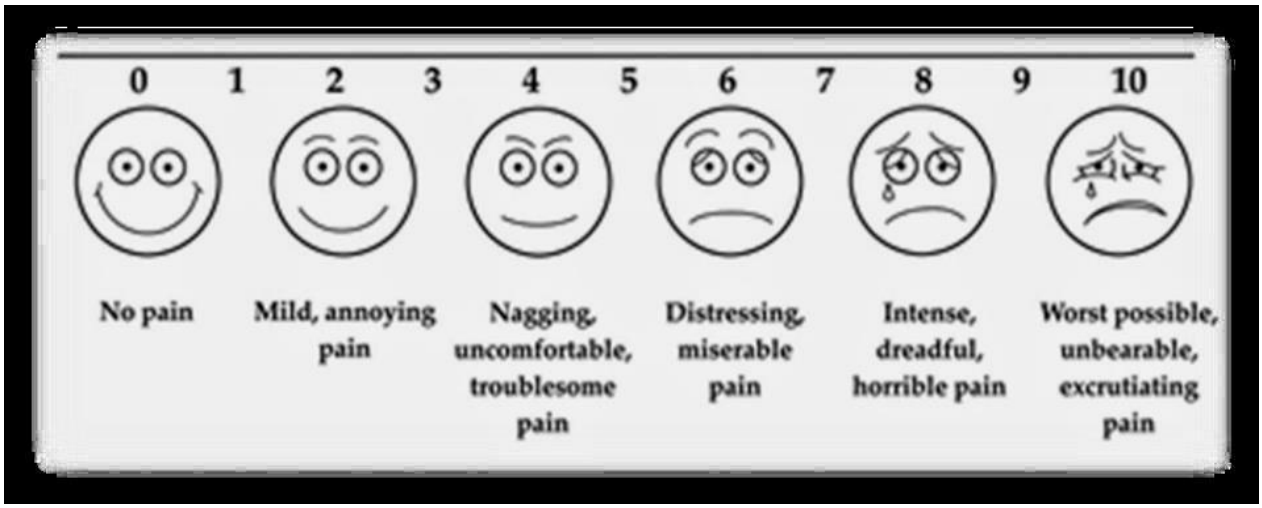


Figure 1: Visual analog scale

Statistical Analysis:

- After collecting the data, all the variables were examined for outliers and non-normal distributions.
- The Categorical variables were expressed as Frequency and Percentage.
- The Quantity variables are expressed as mean and standard deviation.
- Descriptive statistics are used to evaluate baseline characteristics.
- Student's t-test was used to analyse the parametric data, and discrete (categorical) variables were analysed using the Chi-Square test, with a $p < 0.05$ considered statistically significant.
- Results were statistically analysed using SSPS 21 version statistical program for Microsoft Windows

Materials:

1) Transdermal Fentanyl Patch
2) Transdermal Buprenorphine Patch

Figure 2: Transdermal fentanyl patch

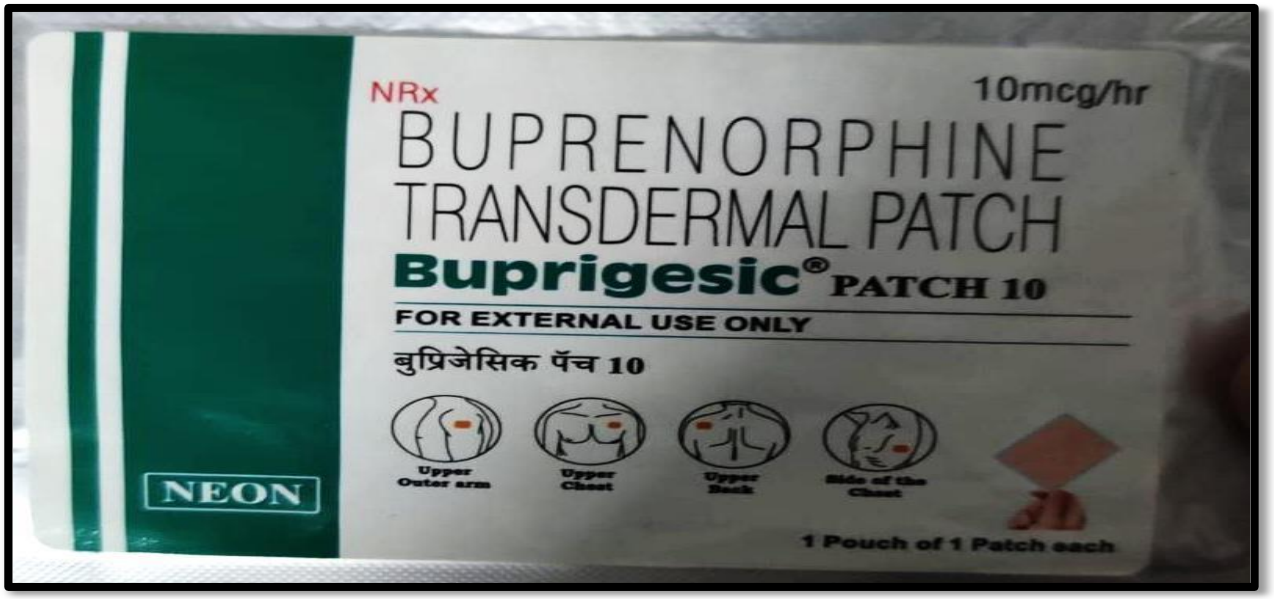


Figure 3: Transdermal buprenorphine patch

SAMPLE SIZE ESTIMATION
Samplesizeformula

$$n = \frac{2(z_{\alpha/2}+z_{1-\beta})^2(\sigma)^2}{\Delta^2}$$

$n = 2(2.58+1.282)^2(0.56)^2$
$(0.46)^2$
$n = 45$

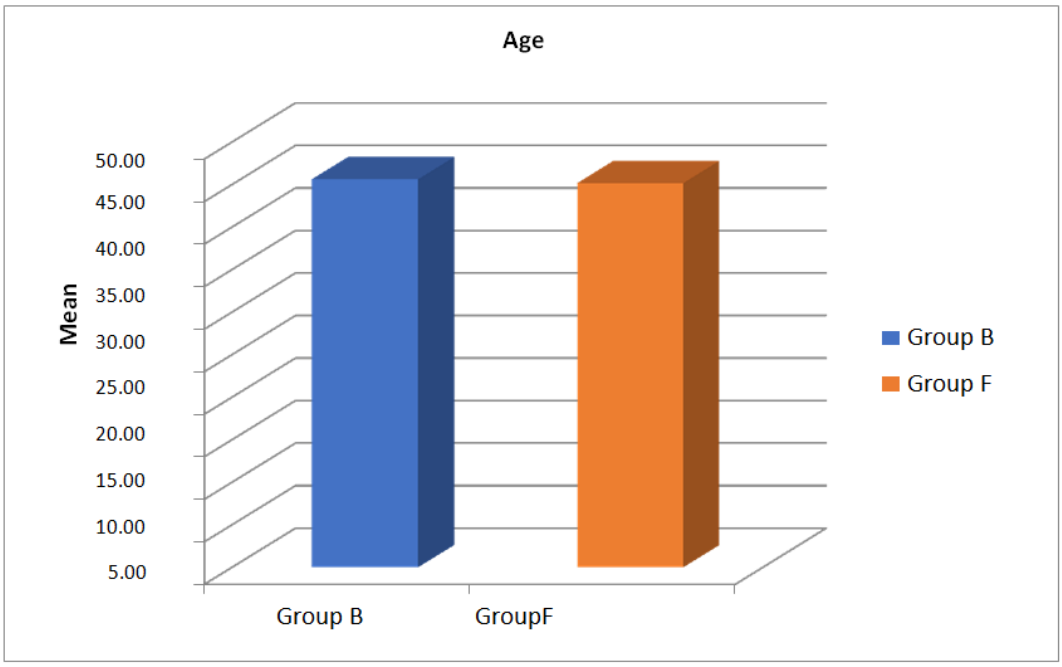
Δ^2-mean difference=0.46
$z_{\alpha/2}$-2.58 standard normal variateat 99%confidence interval $z_{1-\beta}$- 1.282 at 90% power
σ=SD=pooled standard deviation =0.56
n=45 is the minimum sample size for each group. Total sample size = 90 with each group having 45 patients

RESULTS
DEMOGRAPHICPROFILE: AGE

Table 1: Comparison of Age between Group B and Group F

	Group B		**GroupF**		**Z**	**p-value**
	Mean	**SD**	**Mean**	**SD**		
Age	45.62	11.24	45.18	6.71	-0.878	0.380 (Notsignificant, p >0.05)

Mean age of Group B was 45.62 years and Group F was 45.18 years. When these two groups were compared, p value was 0.380 which is statistically insignificant.



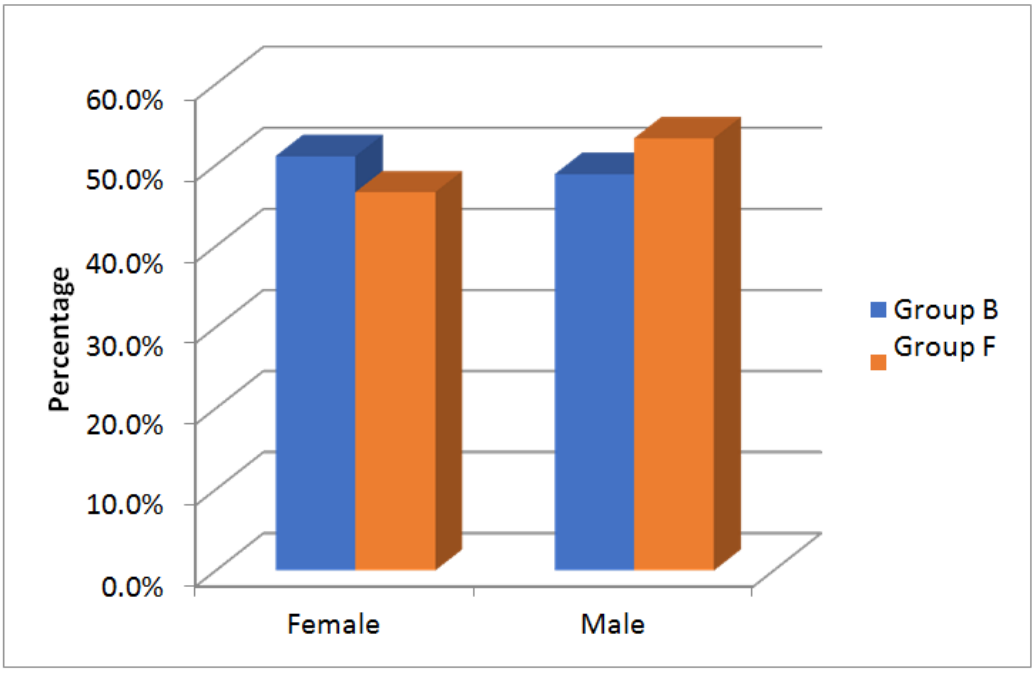
Graph 1: Comparison of Age between Group Band GroupF

GENDER

Table 2: Comparison of Gender between Group Band GroupF

		Group B		GroupF		Total	Chi-Square value	p-value
		No. ofcases	% Age	No. ofcases	% Age			
Gender	Female	23	51.1%	21	46.7%	44	0.178	0.673 (Notsignificant, p >0.05)
	Male	22	48.9%	24	53.3%	46		
Total		45	100.0 %	45	100.0 %	90		

Number of females in group B was 23 and in group F was 21 Number of males in Group B was 22 and in group F was 24. With a p-value of 0.673, the comparison between both groups is statistically insignificant



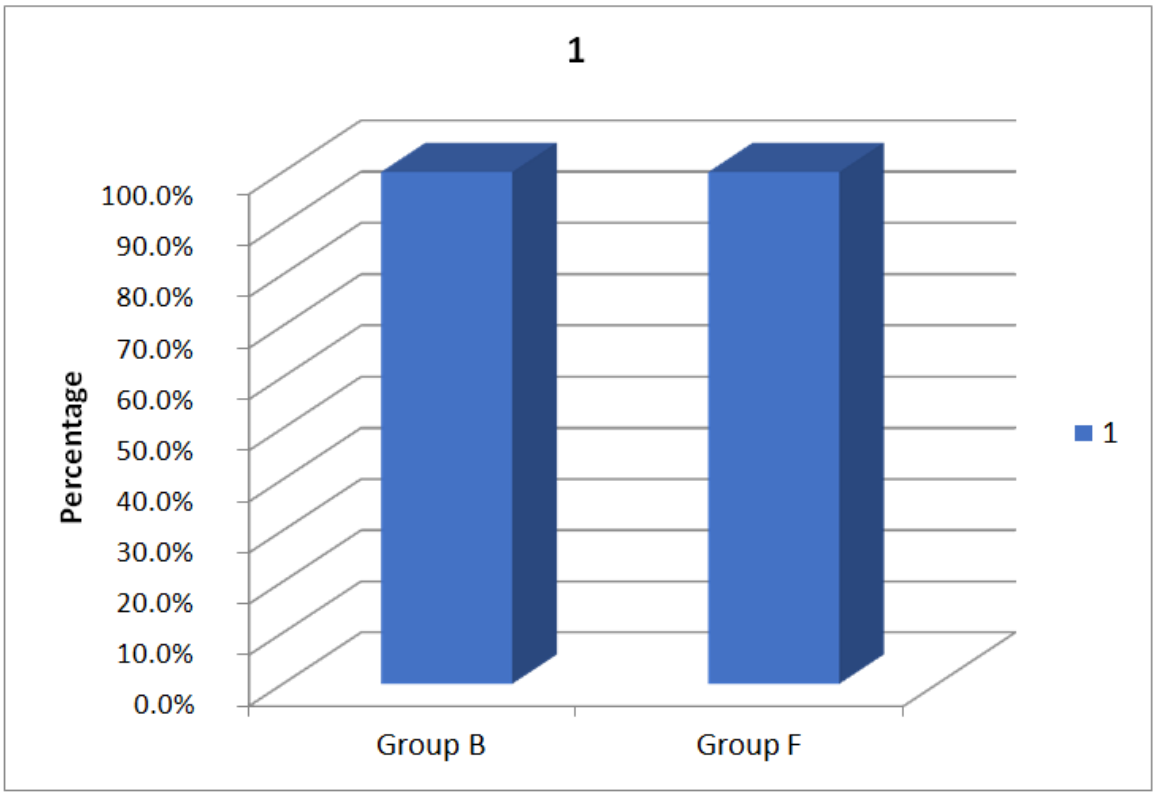
Graph 2: Comparison of Gender between Group Band GroupF

ASA Status

Table 3: Comparison of ASA Status between Group Band Group F

		Group B		GroupF		Total	Chi- square value	p-value
		Group B	Group B	Group F	Group F			
ASAStatus	1	45	100.0%	45	100.0%	90		

All the patients were in ASA 1 status.



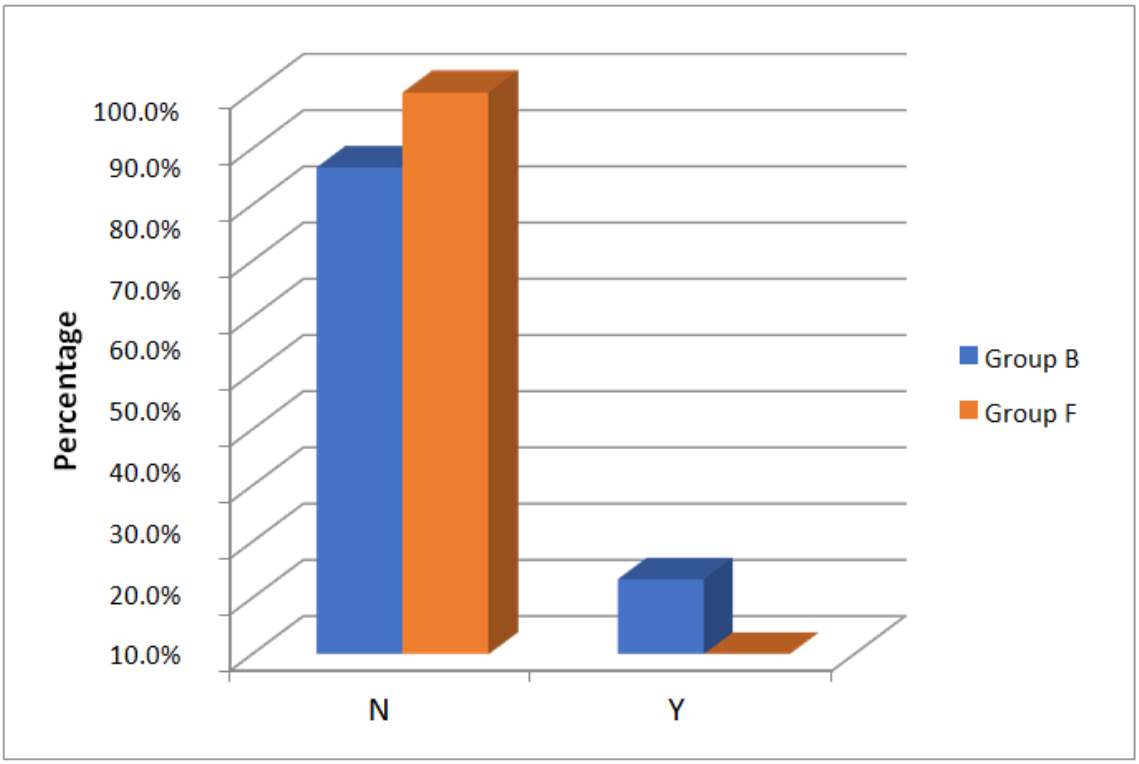
Graph 3: Comparison of ASA Status between Group Band Group F

RESCUE SEDATION

Table 4: Comparison of Rescue Analgesia between Group Band Group F

		Group B		**GroupF**		**Total**	**Chi-square value**	**p value**
		Group B	**Group B**	**Group F**	**Group F**			
Rescue analgesia (Y/N)	N	39	86.7%	45	100.0%	84	6.429	**0.026 (Significant, p <0.05)**
	Y	6	13.3%	0	0.0%	6		
Total		45	100.0%	45	100.0%	90		

6 out of 45 patients required Rescue Analgesia in Group B and no patientsrequiredRescue Analgesia in Group F. When two groups were compared, p value was 0.026 which is statistically significant.



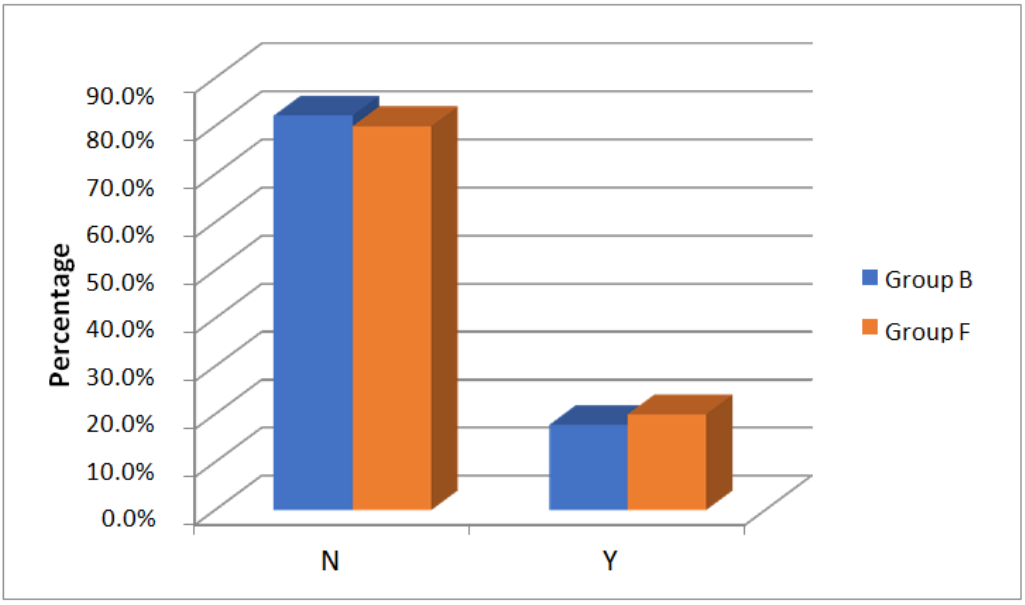
Graph 4: Comparison of Rescue Analgesia between Group Band GroupF

ADVERSE EFFECTS

Table 5: Comparison of Adverse Effects between Group Band Group F

		Group B		**GroupF**		**Total**	**Chi-squarevalue**	**p-value**
		Group B	**Group B**	**Group F**	**Group F**			
Adverse effects(Y/N)	N	37	82.2%	36	80.0%	74	0.304	0.581 (Notsignificant, p >0.05)
	Y	8	17.8%	9	20.0%	16		
Total		45	100.0%	45	100.0%	90		

8 out of 45 patients in Group B and 9 out of 45 patients in Group F experienced adverse effects. When both the groups were compared, p value was 0.581 which is statistically insignificant.



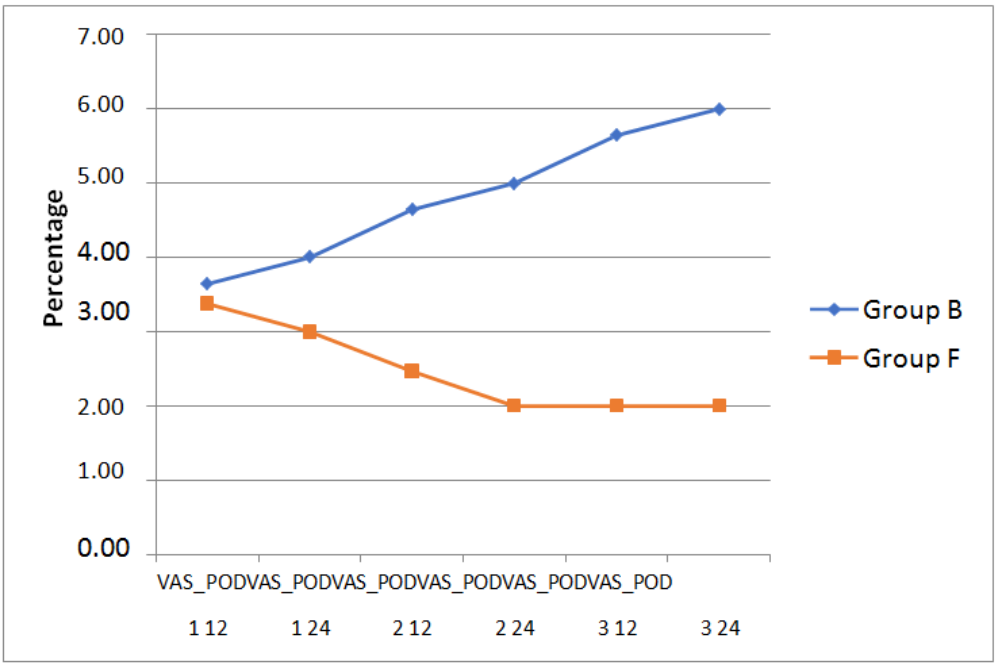
Graph 5: Comparison of Adverse Effects between Group Band GroupF

VAS Score

Table 6: Comparison of VAS between Group Band Group F

	Group B		GroupF		Z	p-value
	Mean	SD	Mean	SD		
VAS_POD112 Hourly	3.64	0.48	3.38	0.49	-2.516	**0.012**
VAS_POD124 Hourly	4.00	0.00	3.00	0.00	-9.434	**0.001**
VAS_POD212 Hourly	4.64	0.48	2.47	0.50	-8.475	**0.001**
VAS_POD224 Hourly	5.00	0.00	2.00	0.00	-9.434	**0.001**
VAS_POD312 Hourly	5.64	0.48	2.00	0.00	-8.936	**0.001**
VAS_POD324 Hourly	6.00	0.00	2.00	0.00	-9.434	**0.001**

When VAS score was compared between two groups at different time intervals, p value was <0.05 and so the results were statistically significant.



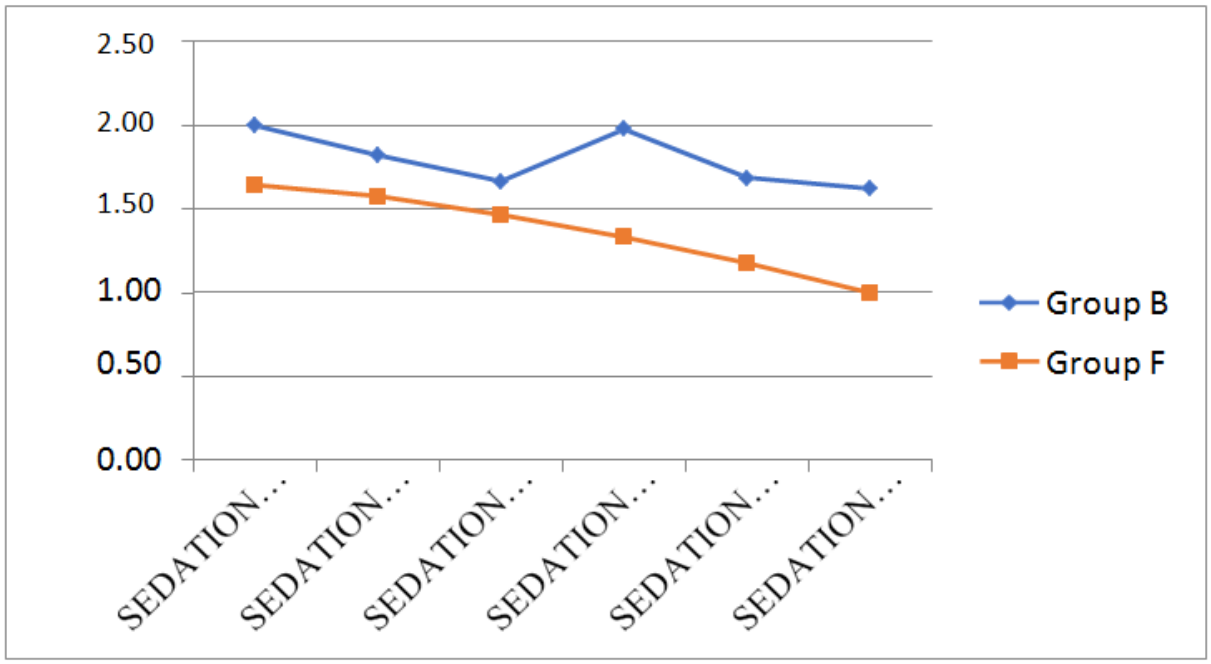
Graph 6: Comparison of VAS between Group Band GroupF

SEDATION SCORE

Table 7: Comparison of Sedation Score between Group Band Group F

	Group B		**GroupF**		**Z**	**p-value**
	Mean	**SD**	**Mean**	**SD**		
SEDATION SCORE_POD 1 12Hourly	2.00	0.00	1.64	0.001	-4.387	**0.001**
SEDATION SCORE_POD 1 24Hourly	1.82	0.39	1.58	0.012	-2.516	**0.012**
SEDATION SCORE_POD 2 12Hourly	1.67	0.48	1.47	0.050	-1.904	**0.050**
SEDATION SCORE_POD 2 24Hourly	1.98	0.15	1.33	0.001	-6.397	**0.001**
SEDATION SCORE_POD 3 12Hourly	1.69	0.47	1.18	0.001	-4.865	**0.001**
SEDATION SCORE_POD 3 24Hourly	1.62	0.49	1.00	0.001	-6.340	**0.001**

When Sedation score was compared between two groups at different time intervals, p value was <0.05 and so the results were statistically significant.



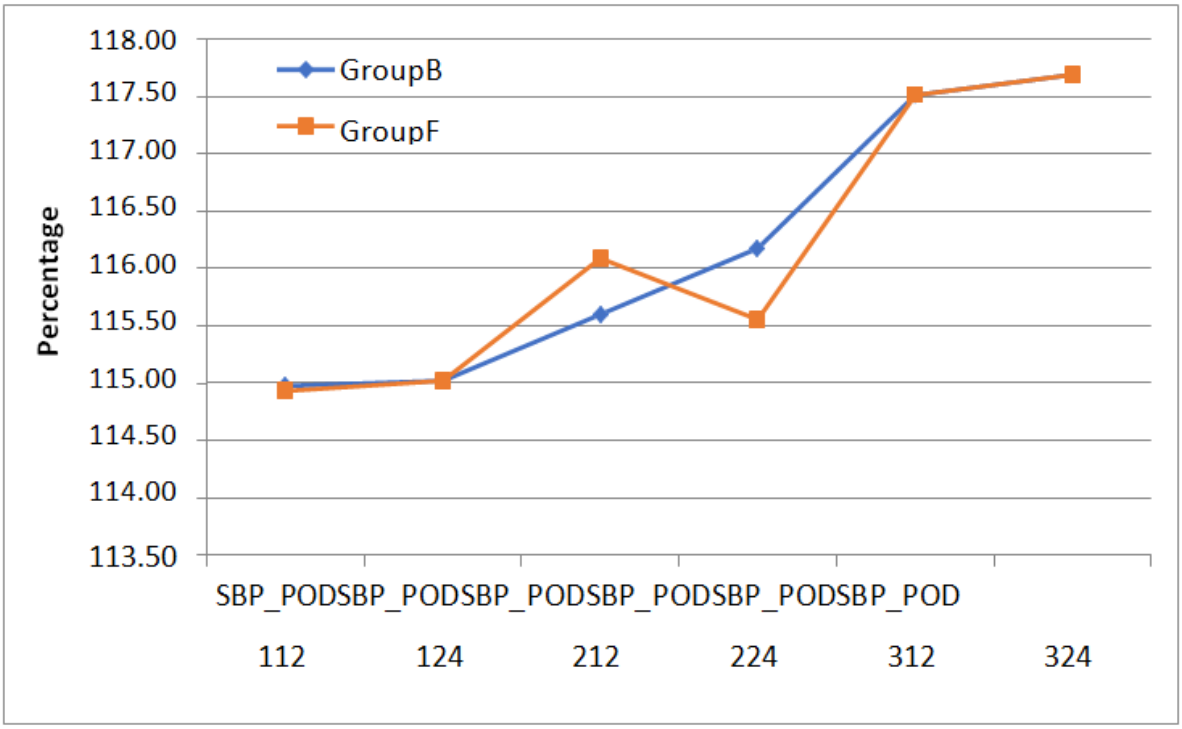
Graph 7: Comparison of Sedation Score between Group Band GroupF

SBP

Table 8: Comparison of SBP between Group Band GroupF

	Group B		GroupF		Z	p-value
	Mean	SD	Mean	SD		
SBP_POD112 Hourly	114.98	1.32	114.93	1.39	-0.103	0.918
SBP_POD124 Hourly	115.02	1.32	115.02	1.32	0.000	1.000
SBP_POD212 Hourly	115.60	1.39	116.09	1.35	-1.612	0.107
SBP_POD224 Hourly	116.18	1.40	115.56	1.47	-1.909	0.056
SBP_POD312 Hourly	117.51	1.42	117.51	1.42	0.000	1.000
SBP_POD324 Hourly	117.69	1.35	117.69	1.35	0.000	1.000

When SBP was compared between two groups at different time intervals, p value was >0.05 and so the results were statistically in significant.



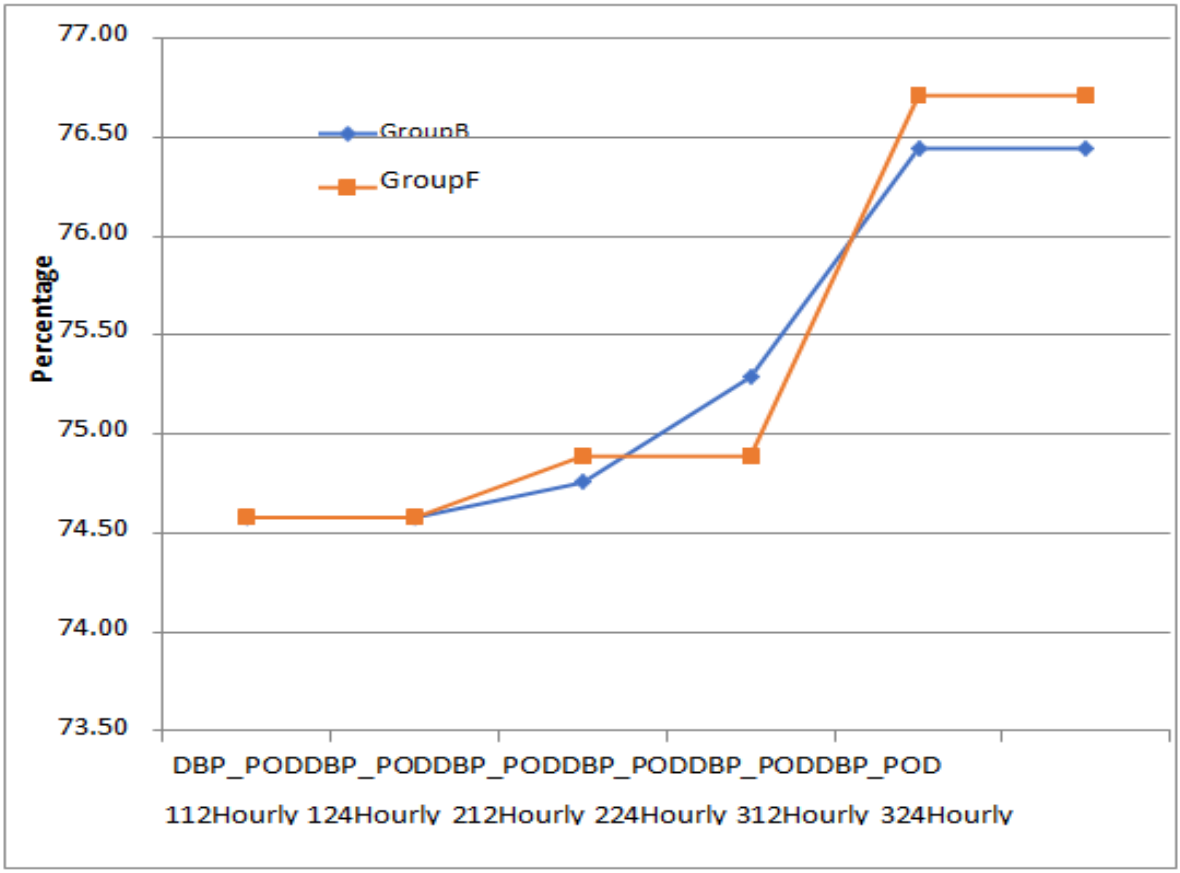
Graph 8: Comparison of SBP between Group Band GroupF

DBP

Table 9: Comparison of DBP between Group Band GroupF

	Group B		GroupF		Z	p-value
	Mean	SD	Mean	SD		
DBP_POD112 Hourly	74.58	2.16	74.58	1.000	0.000	1.000
DBP_POD124 Hourly	74.58	2.16	74.58	1.000	0.000	1.000
DBP_POD212 Hourly	74.76	2.19	74.89	0.761	-0.304	0.761
DBP_POD224 Hourly	75.29	2.34	74.89	0.501	-0.674	0.501
DBP_POD312 Hourly	76.44	2.08	76.71	0.556	-0.589	0.556
DBP_POD324 Hourly	76.44	2.08	76.71	0.556	-0.589	0.556

When DBP was compared between two groups at different time intervals, p value was >0.05 and so The results were statistically insignificant.



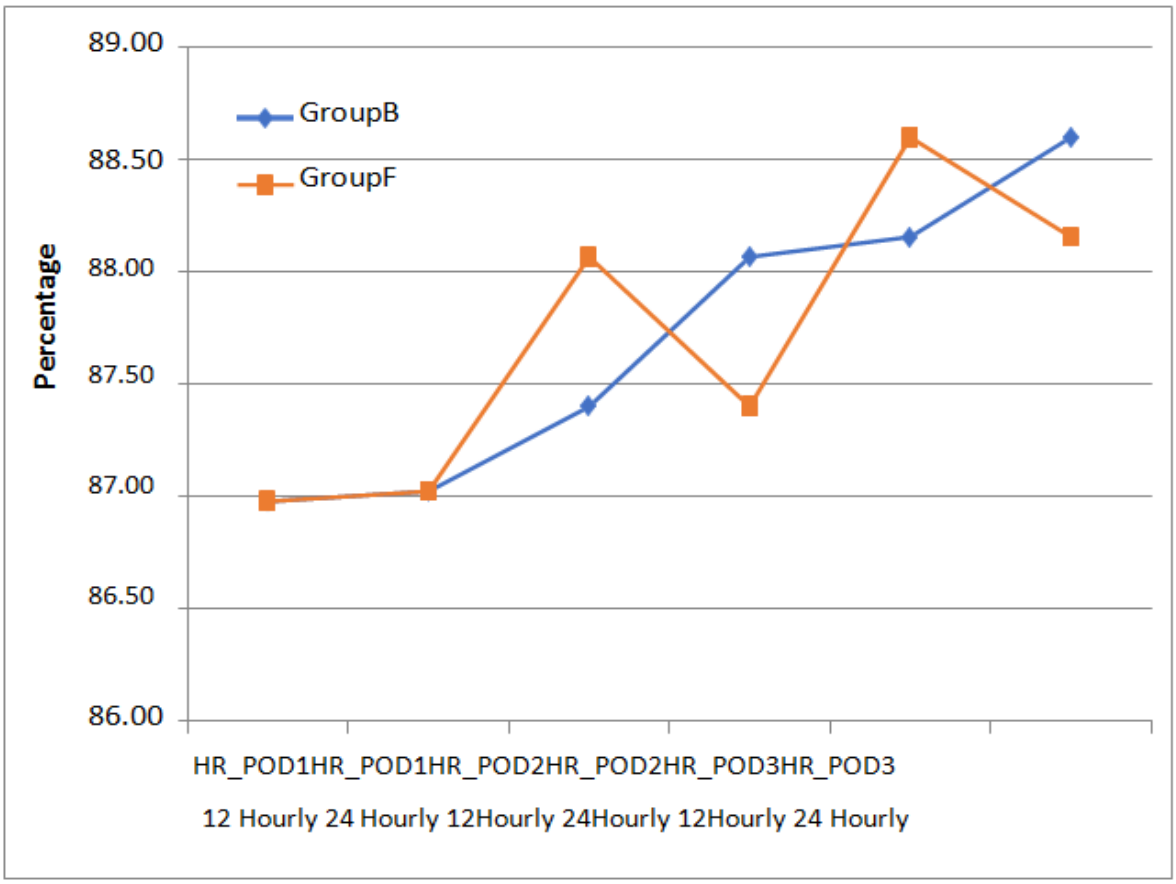
Graph 9: Comparison of DBP between Group Band Group F

HR

Table 10: Comparison of HR between Group B and Group F

	Group B		GroupF		Z	p-value
	Mean	SD	Mean	SD		
HR_POD 1 12 Hourly	86.98	2.15	86.98	2.15	0.000	1.000
HR_POD 1 24 Hourly	87.02	2.17	87.02	2.17	0.000	1.000
HR_POD 2 12 Hourly	87.40	2.30	88.07	2.23	-1.371	0.170
HR_POD 2 24 Hourly	88.07	2.23	87.40	2.30	-1.371	0.170
HR_POD 3 12 Hourly	88.16	2.33	88.60	2.41	-0.986	0.324
HR_POD 3 24 Hourly	88.60	2.41	88.16	2.33	-0.986	0.324

When HR was compared between two groups at different time intervals, p value was >0.05 and so the results were statistically insignificant.



Graph 10: Comparison of HR between Group Band GroupF

DISCUSSION

The goal of the study was to compare the analgesic efficacy of transdermal buprenorphine and transdermal fentanyl for postoperative pain relief.

The dosage of each drug was decided after careful review of the various studies which use different doses of both buprenorphine and fentanyl by transdermal route and the effects of the different doses.

It was observed that 10 $\mu g/hr$of trans dermal buprenorphine and 25µg/hour of transdermal fentanyl had equianalgesic potency when compared to the standard drug morphine [7-40].

A total of 90 patients who were posted for elective major lower limb surgeries and who gave their informed consent, were enrolled in the study.

The patients were allotted into two groups. As it was a single blinded study, only the patient did not know which group they belonged to. Further they were categorized into either group B which received transdermal buprenorphine patch and group F which received transdermal fentanyl patch.

During the pre-anaesthetic evaluation, all the patients were taught the visual analogue scale (VAS) and how to identify adverse reactions e.g. erythema rashes if any occurred. Pre-operative VAS score was noted respective patch was then applied onto a clean, hairless, dry area on the upper chest/back. If there was no area free of hair, then the hair over the chest was clipped with scissors and the patch was firmly held over the skin for 30 seconds. Patients were educated on the care to be takenwhile on the patch and a patient information leaflet was also provided.

Comparison of the age between the two groups showed that the age in both the groups were similar and so the result was statistically not significant.

Comparison of Gender between two groups showed no statistical significance between both the groups.

The comparison of the postoperative VAS scores was done every 12 hourlyfor 3 consecutive days and the result was statistically significant with Group Fentanyl having lower VAS scores compared to Group Buprenorphine on all the 3 days.

On the second and third postoperative days, there was a statistically significant difference in the VAS scores with Group Fentanyl having relatively lower scores compared to group Buprenorphine having higher scores throughout the day. This concludes that transdermal fentanyl takes around 16-18 hours to reach maximum serum concentrations and has better analgesic effect when compared tobuprenorphine.

Also on comparison of baselines VAS scores on day 1,2 and 3, the VASscores were significantly increasing in Group Buprenorphine compared to Group Fentanyl which suggests that Fentanyl is more effective in controlling Postop surgical pain.

The findings of our study were in accordance with the studies done by Z. Arshad, R. Prakash and S. Gautam, in which they found that mean VAS scores were significantly lower in the fentanyl group when compared to the buprenorphine group on postoperative days 1, 2 and 3.

On the second postoperative day, two patients and on third postoperative day, four patients required inj. diclofenac 75mg I/V from group Buprenorphine as rescue analgesic compared to none in group Fentanyl. This corresponds with good postoperative pain relief with transdermal fentanyl patch.

The findings of our study were in accordance with the studies done by Z. Arshad, R. Prakash and S. Gautam, in which they found that the need for rescue analgesia was higher in the buprenorphine group (6 out of 30) when compared to the fentanyl group (0 out of 30) [35].

Comparison of the Ramsay sedation score between the two groups showedthat there was statistically significant change or drop in Ramsay sedation score in Group Fentanyl compared to Group Buprenorphine. Despite of fall, Ramsay sedation scores were higher in Group Buprenorphine compared to Group Fentanyl. All patients in both groups were calm, comfortable and easily arousable throughout the study and none of them showed excessive sedation.

Comparison of the Systolic blood pressure and Diastolic blood pressure showed no statistically significantdifferencebetween the two groups. This shows that transdermal patches as such had no significant impact on the blood pressure.

Comparison of the heart rate between two groups showed no statistically significant difference. This shows that transdermal patches as such had no significant impact on the heart rate.

The incidence of nausea and vomiting was 20% patients in group Fentanyl and 17.8% patients in Group Buprenorphine but was not statistically significant. InjOndansetron 4mg was given to stop nausea and vomiting. No other adverse effects like erythema, rashes were seen.

Our study was comparable to the study conducted by Wolff RF, Reid K, Di Nisio*et al*., where they found that there were fewer side effects in patients who received Transdermal Buprenorphine compared to those who received Transdermal Fentanyl.

CONCLUSION

Based on the findings of our the study we conclude that for post operative pain relief using Fentanyl 25mcg/hr administered 12 hr prior to surgery provides better and effective analgesia, when compared to transdermal buprenorphine 10mcg/hr with minimal side effects.

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