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Transdermal patch of fentanyl for Post-operative Analgesia in Patients Undergoing Elective Abdominal Hysterectomy

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Abstract

Background: Trans-dermal patch of Fentanyl (TPF) was traditionally being utilized for chronic pain. There are limited number of studies on its use in acute postoperative pain. In order to ascertain the effectiveness and safety of TPF for acute postoperative analgesia in patients undergoing abdominal hysterectomy, we therefore designed this study. **Materials And Methods:** This was a randomized controlled research done at our hospital with 44 individuals who came in for an elective abdominal hysterectomy. Two groups were randomly assigned- fentanyl and placebo and followed for 48 hours postoperatively where Numerical rating score (NRS), time to first rescue analgesia, total requirement of rescue analgesics, hemodynamic parameters, sedation, and side effects were noted from 0 min to 48 hours. **Results:** TPF group showed lower NRS scores at 6, 12, 24 and 36 hours which was significant statistically. Additionally, there was a prolonged first rescue analgesic administration and the total requirement of rescue analgesia was less with TPF compared with the placebo group in the first 48 hours which was a statistically significant difference. There was no significant difference related to secondary outcomes & side effects between these two groups statistically. **Conclusion:** Transdermal patch of fentanyl offers effective post-operative pain relief, hemodynamic stability, with no side effects in patients undergoing total abdominal hysterectomy and it can be used when using multimodal analgesia.

Keywords: Transdermal patch of fentanyl, Intravenous Paracetamol, postoperative analgesia, Abdominal Hysterectomy

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Introduction

Adequate pain management using multimodal approach during surgery and in postoperative period offers advantage of accelerated functional recovery and early resumption to normal activity.[1]Acute pain causes diaphragmatic splinting which may predispose to atelectasis and pneumonia .Postoperative pain can delay mobilization, increase chances for deep vein thrombosis and if left untreated, raises the chance of developing chronic pain syndromes, lowers patient satisfaction, and increases healthcare costs.[2]

Transdermal drug delivery is an advanced pain management system with advantages like non-invasive dosing, lack of first- pass metabolism and maintaining sustained blood level of drug. It avoids side effects associated with repeated doses and increases compliance.[3] Fentanyl, is lipid-soluble synthetic opioid and as transdermal patch provides continuous drug delivery and constant plasma concentration yet more research is needed to fully understand its usefulness in treating post-operative pain.[4,5] Thus, we created this study for ascertaining the efficacy and safety of transdermal patch of fentanyl (TPF) for postoperative pain relief in patients posted for elective abdominal hysterectomy.

Our primary objectives were to evaluate the Pain score by Numerical rating scale (NRS), time to 1st rescue analgesic and requirement of rescue analgesics in first 48 hours. Hemodynamic vitals - pulse rate, blood pressure, respiratory rate, SpO2 and incidence of side effects like sedation, respiratory depression, nausea, vomiting, pruritis and skin rash were secondary objectives.

Materials And Methods

This was a hospital based double-blind randomized controlled trial conducted on 44 patients undergoing elective abdominal hysterectomy after institutional Ethics Committee approval (IEC No.: 89/2021) and written and informed consent. The sample size was determined considering the difference in mean NRS score in between the 2 groups as the main outcome measure. Following assumptions were made from the study by Sangineni K.S.D. *et al.* (2016) [2]

Mean +/- Standard Deviation NRS in group 1= 4.2 +/- 1.0, Group 2 = 5.6 +/- 0.9, Effect size (mean difference = 1.4), Alpha error (2 sided) = 1%, Power (1- Beta) = 99%.

$$n = \frac{2s_p^2\left[Z_{1-\alpha/2}+Z_{1-\beta}\right]^2}{\mu_4^2}$$

$$S_p^2 = \frac{s_1^2+s_2^2}{2}$$

Where,

s_1^2: Standard deviation in the first group

s_2^2: Standard deviation in the second group

μ_4^2: Mean differnce between the samples

α: Singnificance level

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Table 1

Inclusion criteria	• Age- 30-60years
	• ASA 1 and 2
	• BMI less than or equal to 30 kg/m2
	•
	• Patients willing to participate in the study
Exclusion criteria	• History of substance abuse
	• Known drug allergy
	• Skin allergy
	• Severe hepatic or renal dysfunction
Withdrawal criteria	• Patients requiring general anaesthesia

Patients were divided into two groups using an opaque, sealed envelope and a computer-generated randomization sequence-

Group 1(study) Fentanyl patch -25 mcg/hr

Group 2 (control) placebo patch.

In both groups patch was applied 3 hrs before surgery. Patients were given spinal anaesthesia with 3.4cc of 0.5% hyperbaric Bupivacaine as per institutional protocol and were monitored intraoperatively with ECG, Systolic, Diastolic, mean blood pressure, pulse rate, respiratory rate, & SpO_2. Inj. Paracetamol 1g was given during abdominal closure and then 12 hourly in postoperative period in both groups for 48 hours. In post-operative period: hemodynamic parameters, pain by Numerical Rating Scale (NRS score) [6], time to first rescue analgesia, , Sedation with Ramsay sedation score(RSS)[7] and adverse reactions like nausea, vomiting, pruritis, skin rash and Respiratory depression (when RR<8/min) were noted at 0 min, 30 mins, 1hour , 2 , 4 , 6 , 12 , 24 , 36 and 48 hours. Analgesia was considered adequate if the NRS score was <4. Diclofenac sodium 75 mg IV in 100 ml of normal saline was administered as the rescue analgesic and total rescue analgesics required in 48 hours were noted.

Statistical Methods

STATA version 10.1 (2011) was statistical program used to code and analyze the data. For qualitative variables, descriptive statistics included the mean and standard deviation. Inferential statistics comprised of tests of significance and P-values. 2 independent samples T-test were used for comparing mean across the groups at various time intervals. To compare mean difference within the group, a Paired T-test was employed. Using the chi-square test comparison of the proportionate differences between two groups was done. It is considered statistically significant when P-value is less than 0.05.

Results

Regarding demographic variables, no statistically significant difference was observed among the 2 groups($p > 0.05$). [Tabel 2].

Table 2: Comparison of Baseline Demographic Characters

S.No	**Variables**		**Group-1 (n = 22)**		**Group-2 (n = 22)**		**P-Value**
			Mean	S.D	Mean	S.D	
1	Age		43.31	3.84	45.45	4.79	0.10
2	Weight		61.86	6.35	59.68	6.57	0.26
3	Height		155.59	2.21	155.72	2.34	0.85
4	BMI		25.62	2.84	24.72	2.64	0.28
5	ASA(Number	*I*	16 (72.7 %)		15 (68 %)		0.37

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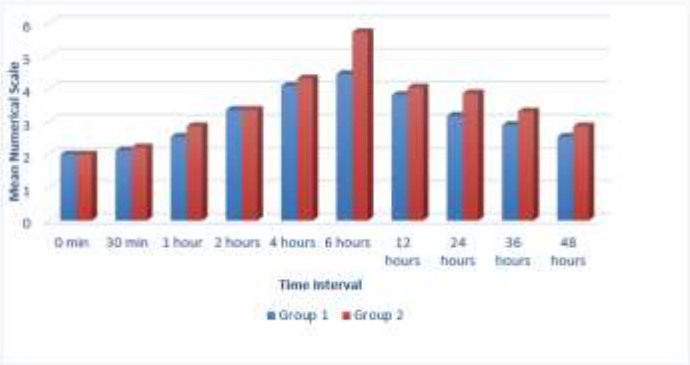
	& percentage)	*II*	6 (27.3 %)	7 (32 %)	

Mean NRS (Graph 1) in group 1 at 6, 12, 24, 36 & 48 hours was less as compared to group 2 (p value- 0.00, 0.05, 0.00, 0.02, 0.01 respectively).



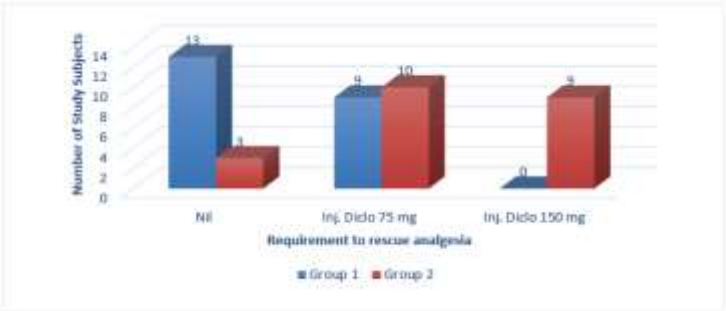
Graph 1: Comparison of Numerical Rating Scale Score in between Two Groups at Various Time Interval (n = 22)

There was a statistically significant difference between the two groups for the
Table 3- In Group 1, majority of study subjects 13 (59 %) didn't require rescue analgesia compared to only 3 patients (13.6 %) in Group 2. In group 1 only 3 patients (13.7%) required rescue analgesia while in group 2, 7 patients (31.8 %) required rescue analgesia within 4 hours. In group 2, 12 patients (54.6 %) required rescue analgesia within 6 hours compared to only 6 pts in group 1. The data indicates a substantial statistical difference ($p < 0.05$) in between the 2 groups.

Table 3: Comparison of Time to First Rescue Analgesia between Two Groups (n = 22)

Time to First Rescue Analgesia	Group 1	Group 2
Nil	13 (59%)	3(13.6%)
4 hours	3(13.7)	7(31.8)
6 hours	6(27.3)	12(54.6)
Total	22 (100)	22(100)
P value- 0.007		

Graph 2- In group 2, out of the 19 patients requiring rescue analgesia, 10 (45.4 %) required inj. Diclofenac 75 mg & 9 (41 %) patients required inj. Diclofenac 150 mg in first 48 hours. In group 1, no rescue analgesia required in 13 patients and 9 patients required only single dose of inj. Diclofenac 75 mg in 48 hours. A statistical significant difference($p < 0.05$) was shown by both groups.



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Graph 2: Comparison of the Total Requirement of Rescue Analgesia in the First 48 Hours between Two Groups. (n = 22) P value-0.000

No statistically significant difference was found in 2 groups, according to the study in terms of mean pulse rate, systolic and diastolic blood pressure, respiratory rate, SpO2 levels, and RSS ($p > 0.05$). Regarding other adverse effects, respiratory depression, nausea, vomiting, pruritis and skin rash were not observed in either group.

Discussion

Adequate postoperative analgesia is necessary for safe and timely discharge of the patient.[8] TPF provides a prolonged analgesic effect due to high affinity for narcotic receptors [9] and eliminates the pharmacokinetic issues associated with oral and parenteral administration.[10,11,12].Keeping in mind TPF pharmacokinetics , we applied patch 3 hours prior to the surgery.

The two groups showed statistically significant difference for the mean NRS at 6, 12, 24, 36 & 48 hours ($p < 0.05$) in our study. Similarly, Sathitkarnmanee *et al.*[13] found significantly lower NRS both while resting and during movement over the period of 48 hours in the TPF group (mean = 2.73, SD = 1.95) as compared to the Placebo group (mean = 4.64, SD = 1.6) ($p < 0.05$).

The study done by Rallabhandi S, *et al.*[14] showed that mean pain scores over 24 hours post-operatively were significantly lower in Group TPF (3.80 ± 0.12) than Group Intravenous(IV) fentanyl (4.67 ± 1.18) (p - 0.012). Gupta R.*et al.* [1] found lower scores in group III (5mg TPF) and group II (2.5mg TPF) & the mean difference showed statistical significance (P = 0.00) after 90 min.

However in a study by Merivirta *et al.*,[15] the difference was not statistically significant in pain scores between TPF 12 mcg/hr and placebo groups (P = 0.91) for 4 post-operative days, might be because of the lower concentration of patch used.

In present study, 13 patients (59 %) in Group 1 didn't require rescue analgesia compared to only 3 patients (13.6 %) in Group 2. In group 2, 12 patients (54.6 %) required rescue analgesia within 6 hours compared to only 6 patients in group 1. The mean time for 1st rescue analgesia was 354 minutes in group 1 and 226 minutes in group 2, which was considered statistically significant. ($p < 0.05$).

The study by Rallabhandi S.*et al.* [14] mean time for first rescue analgesia (minutes) in Group TPF (345.50 ± 33.34) was significantly longer than Group IV fentanyl (58.10 ± 12.88) ($p < 0.001$) showing that the difference between 2 groups was significant.

Hosseini *et al.*[16] noted that the mean time for first rescue analgesic in FTD group was significantly greater than placebo group (FTD 367.7 ± 349.7 minute vs. placebo 59 ± 13.88; P = 0.04).

Gupta R.*et al.* [1] observed that the mean time to first rescue analgesic in group III (5mg TPF) was 4320 ± 0 mins, 4112 ± 930.65 mins in group II(2.5mg TPF). The mean time to first rescue analgesic was shortest i.e. 224.6 ± 43.83 mins in group I (placebo patch) showing statistical significant difference. (P = 0.00).

For Group 2, out of 19 patients requiring rescue analgesia, 10 (45.4 %) required inj. Diclofenac 75 mg & 9 (41 %), patients required inj. Diclofenac 150 mg in first 48 hours. In group 1, 9 patients required only single dose of inj. Diclofenac 75 mg in 48 hours. Group 1 required an average of 75 mg of rescue analgesia, whereas Group 2 required an average of 110 mg ($p < 0.05$), indicating a statistical significant difference.

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In the study by Abrisham *et al.*[17] During the 72 postoperative hours, group I (TPF) consumed considerably less total rescue morphine (33.0 ± 8.6 vs. 40.0 ± 6.8, p = 0.01) than group II (Placebo).

Gupta R.*et al.*[1] found that no patient in group III(5mg TPF), 3 patients in group II(2.5mg TPF), and 19 patients in group I (placebo patch) required rescue analgesics. The difference was found to have a statistical significance. (P = 0.000), which was similar to our findings.

However, in contrast, Merivirta *et al.*[15] observed that although it had no statistical significance, the placebo group used rescue analgesics marginally more frequently than the fentanyl group. Despite being a low dose, the 12 µg/hour fentanyl patch employed in this study did not significantly reduce the usage of rescue opioid.

Throughout the course of our study, the 2 groups didn't show any significant difference statistically among the two groups with respect to parameters like respiratory rate, O2 saturation, heart rate, systolic blood pressure, diastolic blood pressure, and mean blood pressure.

Like findings in our study, Hosseini *et al.*[16] observed the pre and post laparotomy heart rate, systolic, diastolic and mean blood pressure and did not find any significant difference in these parameters (P = 0.86, P = 0.44, P = 0.06 and P = 0.10, respectively).

No patient belonging to patch group needed airway intervention, and the two groups did not show any statistically significant difference in terms of RSS (P > 0.05) in our study.

The results we achieved were consistent with the findings of Sathitkarnmanee *et al.*[13]in which the sedation scores were not significantly different between TPF (mean = 0.27) & Placebo (mean = 0.18) . Neither group experienced any additional side effects, such as skin rash, pruritis, nausea, vomiting, or respiratory depression. These findings were consistent with other studies.

Limitations

The limitations in our study were- small sample size, follow-up only for 48 hours. Plasma levels of the drug were not measured in our study.

Future Research

The true potential of transdermal fentanyl for the management of postoperative pain may be revealed by an earlier application of a fentanyl patch combined with a study of plasma drug levels. To determine the safety profile of fentanyl patches in individuals with concomitant conditions, particularly respiratory problems, further research is required.

Conclusion

Transdermal patch of fentanyl (25 mcg/hr) offers effective postoperative analgesia, hemodynamic stability, without significant side effects. It is safe, non-invasive method and can be used as a part of multimodal analgesia in patients posted for elective abdominal hysterectomy.

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