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ORIGINAL RESEARCH

STUDY TO EVALUATE THE EFFECTIVENESS OF TRANSDERMAL FENTANYL PATCHES FOR POSTOPERATIVE PAIN AFTER CAESAREAN SECTION

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ABSTRACT:

Introduction: Useof transdermal fentanyl patches is increasingly used for chronic pain management because of non-invasive dosing, longer duration of action and minimal side effects. However its role in relieving postoperative pain after caesarean section is not well established.

Aim: To evaluate the effectiveness and safety of transdermal fentanyl patches (Duragesic 50 microgram/hour) for relieving postoperative pain after caesarean section.

Material and methods: A prospective randomized two-arm study was conducted to compare the efficacy and safety of transdermal fentanyl patch 50mcg/hr for post-operative pain relief after elective cesarean section. After institutional approval and written informed consent, 70 female patients coming for elective cesarean section were selected, 35 patients were randomly allocated to each group. Group A received transdermal fentanyl patch and group B received placebo patch.

Results: There was no difference in demographic data between the two groups. Pain scores as well as requirement of rescue analgesia was less in the study group compared to the control group.

Conclusion: we conclude that transdermal administration of fentanyl 50 µg/h preoperatively is an effective noninvasive and convenient technique for postoperative pain relief after elective caesarean section surgery .

Keywords: Elective caesarean section, placebo patch, Transdermal fentanyl patches.

INTRODUCTION:

For all the happiness man can gain is not in pleasure but in rest from pain.John Dryden. Although post operative pain is arguably the most commonclinical problem in our hospitals,it is often dismissed with an order forintermittent intramuscular opiate injections to be given at the discretion ofan overworked nursing staff. This generally results in patients waiting for painrelief,then a period of relief and perhaps drowsiness, and the cycle isrepeated.With this method,pain relief is only satisfactory (Adequate reliefwithout unwanted sedation) for about one third of the time.Goodpostoperative analgesic management probably carries benefits other than increased patient comfort.The magnitude of the neuroendocrine stressresponse, postoperative pulmonary complications and the incidence ofmyocardial ischemia can be decreased.Early mobilization can be achieved andthe patient can be discharged from the hospital sooner.[1]

Management of postoperative pain in Lower segmental caesareansection(LSCS) parturient is a lot to be desired. It is advocated that the painmanagement has to be for 48 hours after lower abdominal surgery.

Fentanylis a synthetic opioid with short acting analgesic activity afterintravenous or subcutaneous administration.The low molecularweight,highpotency and lipid solubility of fentanyl make it suitable fordelivery via the transdermal therapeutic system(TTS).These systems aredesigned to release the drug in to skin at a constant rate ranging from 25 to100 micrograms/hr, multiple systems can be applied to achieve deliveryrates.Initially ,much of the clinical experience with fentanyl TTS was obtained in patients with acute postoperative pain.[1]

Compared with other opioids, fentanyl patches have been associated with better pain relief, less constipation, lesser incidence of vomiting, good patient accessibility and they enhance the quality of life.

Pain management postpartum is complicated by concerns regarding exposure of the neonate through breastfeeding as well as increased risk of maternal thromboembolism and interference with lactation from sedation. The American academy of pediatrics considers fentanyl use compatible with breastfeeding based on short-term maternal use. Fentanyl levels measured in both breast milk and baby's serum were low .The way for improving postoperative pain management should include procedure specific guidelines, new methods to predict postoperative pain and new drugs and delivery systems .[2]Hence, objective of this study was to determine the safety and effectiveness of a transdermal fentanyl delivery system for the relief of postoperative pain using fentanyl patches (duragesic) 50 microgram/hour following elective caesarean section.

MATERIALS AND METHODS:

It is a Prospective, randomized study on female patients aged between who are Scheduled for elective Caesarean surgeries. The patients were selected based on those satisfying the inclusion criteria. After the approval by the Ethical clearance committee, written informed consent was obtained from all the patients included in the study.

INCLUSION CRITERIA:

Female patients aged between 18-45 years**,** ASA I – II**,** Body mass index (BMI) between 20-25 kg/m^2 **who are** Scheduled for elective Caesarean surgeries.

EXCLUSION CRITERIA:

Patients who have received opioids pre-operatively**,** Contraindication to regional block (coagulation defect, local infection at the site of injection)Patients having moderate or severe renal and hepatic impairment documented history of opioid sensitivity or drug abuse.

In 2-arm study on 70 patients was randomly allocated to two groups of 35 each:

Group A: Patients who received transdermal therapeutic system-fentanyl 50 mg/hour.

Group B: Patients who received transdermal placebo patch

Detailed pre-anesthetic check-up including anticipation of difficult airway was done and patients were counseled regarding sub-arachnoid block (procedure, risks and benefits) and visual analogue scale which is a line graded from 0-10, where 0=no pain and 10=the worst pain imaginable. Patients were pre-mediated with Inj omeprazole 40mg night before and morning of surgery, Inj Ranitidine 50mg i.v. and Inj Metoclopramide 10mg iv, 5 mins prior to surgery. On the day of surgery, before shifting to the operation theatre, an 18 gauge peripheral venous cannula was inserted and patients were preloaded with 500ml of ringer lactate. In the pre-operative room, baseline readings of heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and oxygen saturation were measured. Consent was checked. Monitors such as Non-invasive blood pressure with right sized BP cuff, pulse oximetry, capnography, functional suction tubing, Electrocardiography, were connected. Airway equipments like oral airways, laryngeal mask airway size 3 and 4, different laryngoscope blades and endotracheal tubes sized 6mm-7mm cuffed difficult airway cart and emergency drugs were kept ready. Either fentanyl patches 50 mg/hour or placebo patches were placed on a hair-free area in the antero-lateral chest wall or upper or at the sides of the waist and mounted in place and covered by adhesive plasters. Patients were made to lie down in left lateral decubitus position. After scrubbing and wearing sterile gloves, the skin of the patient's back was painted with Povidone-iodine solution three times and then with spirit. Sterile hole towel was draped over the back. After palpation of the anatomical landmarks, appropriate space (L3-L4 or L2-L3) is localizes. 2 ml of 2% lignocaine was given for skin infiltration. 25 guagequincke's needle was introduced into the sub-arachnoid space and observed for free flow of clear cerebrospinal fluid. 10mg of 0.5% hyperbaric bupivacaine was injected intrathecally following which patients were made to lie down supine and BP recordings mask. The level of the block was checked. Once an adequate block (T6) is achieved, the surgery was started. Intraoperative hypotension was defined as 20% decrease in blood pressure and was treated with intravenous fluids, intravenous blouses of Inj Ephedrine 5-15mg IV or Inj. phenylephrine 25-50 mg iv. Intraoperative bradycardia was defined as 30% decrease from the basal heart rate or heart rate less than 60 beats/minute and was treated with Inj Atropine 0.6mg iv. Immediately after baby extraction, 10 units of Inj Oxytocin was infused along with intravenous fluids to achieve adequate uterine contraction. The neonatologist present in the complex took over the baby and checked for the APGAR score at 0 and 5 minutes. Once the surgery was complete, vitals were checked and patient was shifted to recovery room.

In the recovery room, All the ASA standard monitors like SPO_2, NIBP, and ECG. were connected.PR monitored for 1^{st}, 5^{th}, 10^{th}, 15^{th}, 30^{th} min. patient was monitored for SPO_2, at the 1^{st} min, 5^{th} min, 10^{th} min, 15^{th} min up to 30^{th} mins. And MAP (Mean Arterial Pressure) at

1st, 5th, 10th, 15th, and 30th mins. If any decrease in MAP,ephedrine 5mg intravenously,was given.

Pain was assessed post-operatively at 3rd, 7th, 11th, 15th, 19th, 23rd, 27th, 31st, 35th, 39th, 43rd, 47th, 48th hours using a visual analogue scale (VAS). Where '0' is no pain, 10 is worst pain imaginable, in between 0 & 10, where 1-3 denotes mild pain, 3-6 denotes moderate pain, 6-9 denotes severe pain. If the VAS during any time study was more (or) equal to five ----- injection tramadol 100 mg intravenously was administered intra-vinous as rescue analgesia. Time at which rescue analgesia administered to each group and side effects with the use of study drug were also noted.

Patient was monitored for sedation using Ramsay sedation score (RSS), by this patients were catogorised in to 2 groups where group – 1 is asleep and group – 2 is awake for 4 hours. Patient monitored for any side effects of fentanyl like constipation, respiratory depression, nausea**,** vomiting. If vomiting present ondonsetron 4mg,intravenous was given.

STATISTICAL METHODS:

The difference between two means of visual analogue score is 2 and mean standard deviation is 2. Power of study was conducted with confidence limit of 80% with calculated sample size by allowing an α of 0.001 and β of 0.2 per group is 35. As all the distributions will merge into normal distribution. Sample size i.e… 35 is enough because inference that can be drawn based on 35 observations will less remain the same, in spite of any increase in the sample size. Hence a total of 70 subjects were included in our study and divided into two groups each containing 35 subjects.

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean + SD (Min-Max) and result on categorical measurements are presented in Number (%). Significance is assessed at 5% level of significance. The following assumptions on data are made.Student 1 test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters.

Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

+ Suggestive significance (P value: $0.05<p<0.10$)

+ Moderately significant (P value: $0.01<P<0.05$)

++ Strongly significant (P value: $P<0.01$)

Statistical software: the Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.01, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

RESULTS:

Table-1: Demographic details in present study

Age in years	Group A	Group B	Total	P Value
<20	1 (2.9%)	0 (0%)	1 (1.4%)	
20-30	32 (91.4%)	32 (91.4%)	64 (91.4%)	P=0.893
31-40	2 (5.7%)	3 (8.6%)	4 (5.7%)	

Total	35 (100%)	35 (100%)	70 (100%)	
Mean + SD	25.40 + 3.73	25.51 + 3.31	25.46 + 3.50	
ASA Grade				
Grade I	27 (77.1%)	27 (77.1%)	54 (77.1%)	P=1,000
Grade II	8 (22.9%)	8 (22.9%)	16 (22.9%)	
Duration of Surgery				
1-30	2 (5.7%)	3 (8.6%)	5 (7.1%)	P = 0.220
31-60	33 (94.3%)	32 (91.4%)	65 (92.9%)	
Total	35 (100%)	35 (100%)	70 (100%)	
Mean + SD	40.29 + 6.29	38.71 + 4.08	39.50 + 5.33	

70patients were randomized into two groups A and B of 35 patients each. The mean age in group A was 25.40+3.73 years as against 25.51+3.31 years in group B. This was found to be statistically insignificant .In Group A, 27 patients were ASA I and 8 patients were ASA II. In group B, 27 patients were ASA I and 8 patients were ASA II which was found to be statistically insignificant.The mean duration of surgery was 40.29+6.29 min in group A as against 38.71+4.08 min in group B. Average duration of surgery for both groups was 30-45 minutes. This was found to be statistically insignificant.

Table-2: Pain score in two groups of patients studied

Pain score	Group A (n=35)	Group B (n=35)	Total	P value
3rd hour				
* 0	26(74.3%)	0(0%)	26(37.1%)	<0.001**
* 1-3	9(25.7%)	15(42.9%)	24(34.3%)	
* 4-6	0(0%)	20(57.1%)	20(28.6%)	
* 7-10	0(0%)	0(0%)	0(0%)	
7th hour				
* 0	5(14.3%)	0(0%)	5(7.1%)	<0.001**
* 1-3	23(65.7%)	14(40%)	37(52.9%)	
* 4-6	7(20%)	21(60%)	28(40%)	
* 7-10	0(0%)	0(0%)	0(0%)	
11th hour				
* 0	10(28.57%)	0(0%)	10(14.28%)	<0.001**
* 1-3	19(54.28%)	24(68.57%)	43(61.42%)	
* 4-6	6(17.14%)	11(31.42%)	17(24.28%)	
* 7-10	0(0%)	0(0%)	0(0%)	
15th hour				
* 0	9(25.7%)	0(0%)	9(12.9%)	<0.001**
* 1-3	24(68.57%)	27(77.14%)	51(72.85%)	
* 4-6	2(5.71%)	8(22.85%)	10(14.28%)	
* 7-10	0(0%)	0(0%)	0(0%)	
19th hour				
* 0	8(22.9%)	0(0%)	8(11.4%)	<0.001**

* 1-3	27(77.1%)	27(77.1%)	54(77.14%)	
* 4-6	0(0%)	8(22.9%)	8(11.42%)	
* 7-10	0(0%)	0(0%)	0(0%)	
23rd hour				
* 0	9(25.7%)	0(0%)	9(12.9%)	<0.001**
* 1-3	24(68.57%)	29(82.85%)	53(75.71%)	
* 4-6	2(5.71%)	6(17.14%)	8(11.42%)	
* 7-10	0(0%)	0(0%)	0(0%)	
27th hour				
* 0	17(48.6%)	0(0%)	17(24.3%)	<0.001**
* 1-3	15(42.85%)	25(71.42%)	40(57.14%)	
* 4-6	3(8.571%)	10(28.57%)	13(18.57%)	
* 7-10	0(0%)	0(0%)	0(0%)	
31ST Hour				
* 0	27(77.1%)	0(0%)	27(38.6%)	<0.001**
* 1-3	7(20%)	35(100%)	42(60%)	
* 4-6	0(0%)	0(0%)	0(0%)	
* 7-10	0(0%)	0(0%)	0(0%)	
35th hour				
* 0	29(82.9%)	0(0%)	29(41.4%)	<0.001**
* 1-3	6(17.1%)	31(88.57%)	37(52.85%)	
* 4-6	0(0%)	4(11.42%)	4(5.71%)	
* 7-10	0(0%)	0(0%)	0(0%)	
39th hour				
* 0	28(80%)	0(0%)	28(40%)	<0.001**
* 1-3	5(14.3%)	30(85.71%)	35(50%)	
* 4-6	2(5.71%)	5(14.28%)	7(20%)	
* 7-10	0(0%)	0(0%)	0(0%)	
43rd hour				
* 0	32(91.4%)	0(0%)	32(45.7%)	
* 1-3	2(5.7%)	32(91.42%)	34(48.57%)	<0.001**
* 4-6	0(0%)	3(8.57%)	3(4.28%)	
* 7-10	0(0%)	0(0%)	0(0%)	
47th hour				
* 0	33(94.3%)	0(0%)	35(47.1%)	<0.001**
* 1-3	2(5.7%)	35(100%)	37(52.9%)	
* 4-6	0(0%)	0(0%)	20(28.6%)	
* 7-10	0(0%)	0(0%)	0(0%)	
48th hour				
* 0	35(100%)	0(0%)	35(50%)	<0.001**
* 1-3	0(0%)	31(88.57%)	31(44.28%)	
* 4-6	0(0%)	4(11.42%)	4(5.71%)	

* 7-10	0(0%)	0(0%)	0(0%)	

In 3rd,7th,11th,15th,19th,23rd,27th,31st,35th,39th,43rd ,47th ,48th postoperative hour, all the patients showed a P value of <0.001 statistically significant.

Table-3: Comparison of Pain Score in two groups of patients studied

Pain score	Group A	Group B	P value
3rd hour	0.37+0.69	3.91+1.72	<0.001**
7th hour	2.23+1.55	2.97+1.32	0.035*
11th hour	1.31+1.41	2.69+0.76	0.012*
15th hour	1.03+0.89	2.63+0.49	0.001**
19th hour	0.97+0.66	2.20+0.00	0.012*
23rd hour	0.83+0.57	2.91+0.32	0.012*
27th hour	0.51+0.51	2.01+0.32	<0.001**
31st hour	0.24+0.50	1.98+0.30	<0.001**
35th hour	0.17+0.38	2.00+0.32	<0.001**
39th hour	0.14+0.36	2.10+0.00	<0.001**
43rd hour	0.06+0.24	2.13+0.20	<0.001**
47th hour	0.06+0.24	1.70+0.00	<0.001**
48th hour	0.00+0.00	1.92+0.03	<0.001**

Here is a table comparing mean pain scores every 4th hourly starting from 3rd,7th,11th,15th,19th,23rd,27th,31st,35th,39th,43rd ,47th ,48th postoperative hour showed a P value of <0.001 which was found to be statistically significant.

Table-4: Hemodynamic changes in comparision in both groups

SpO_2	Group A	Group B	Total	P value
1 min	99.40+0.77	99.51+0.70	99.46+0.74	0.520
5 min	99.66+0.64	99.74+0.44	99.70+0.55	0.517
10 min	99.57+0.70	99.66+0.64	99.61+0.67	0.594
15 min	99.66+0.59	99.80+0.41	99.73+0.51	0.243
30 min	99.34+0.73	99.57+0.65	99.46+0.70	0.171
P.R (mm Hg)				
1 min	93.57+14.3	93.4+15.8	0.17	0.97
5 min	91.53+15.38	89.93+14.64	1.6	0.68
10 min	91.23+16.37	88.63+15.25	2.8	0.47
15 min	91.63+15.15	86.3+15.52	5.33	0.18
30 min	90+15.2	83.73+15.39	6.27	0.12
MAP (mm Hg)				
1 min	78.51+9.94	78.09+7.35	78.30+8.68	0.838
5 min	78.71+10.18	77.71+8.96	78.21+9.53	0.664
10 min	77.63+8.59	78.23+9.16	77.93+8.82	0.778
15 min	76.66+7.74	76.51+8.83	76.59+8.24	0.943
30 min	76.11+8.00	77.06+8.70	76.59+8.31	0.638

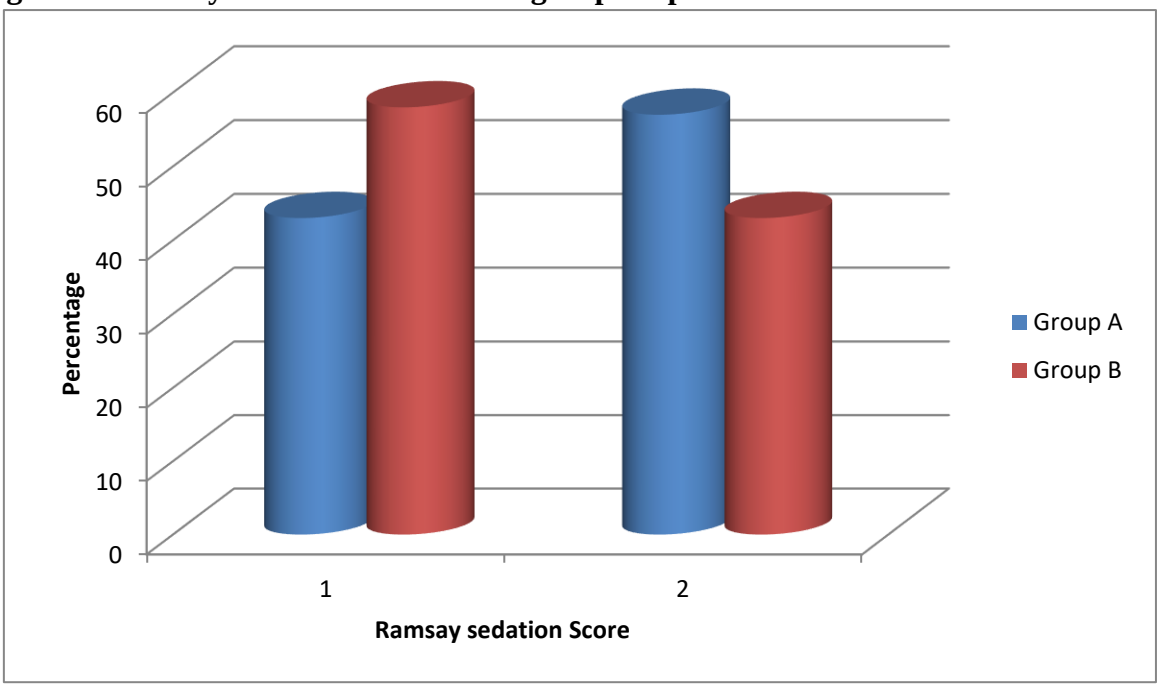
Oxygen saturation in both the groups in the first half an hour did not vary and hence MAP was calculated for both the groups in the first half an hour and it did not vary.Hence, was found to be statistically insignificant.

Table-5: Rescue Analgesia requirement between groups

Rescue Analgesia	Group A	Group B	P Value
3rd hour	10	33	<0.001
7th hour	6	21	<0.001
11th hour	6	11	<0.001
15th hour	2	8	<0.001
19th hour	0	8	<0.001
23rd hour	2	6	<0.001
27th hour	3	10	<0.001
31st hour	0	0	
35th hour	0	4	<0.001
39th hour	2	5	0.012
43rd hour	0	3	<0.001
47th hour	0	0	
48th hour	0	4	<0.001

Requirement of rescue analgesia was more in Group B compared to Group A. In the 3rd,7th,11th,15th,19th,23rd,27th,35th,43rd,48th postoperative hour showed a P value of <0.001 which was found to be statistically significant. 31st,39th,47thpostoperative hour showed which was found to be statistically insignificant

Figure-1: Ramsay Sedation score in two groups of patients studied



P=1.000, Not significant, Fisher Exact test

Ramsay sedation score was checked 3 hours postoperatively in both the groups and the patients had a score of 1-2 which was found to be statistically insignificant.

Table-6: side effects in groups

Side Effects	Group A (n=35)	Group B (n=35)	Total (n=70)	P Value
Nausea				
• Negative	31(88.57%)	35(100%)	66(94.28%)	P<0.05
• Positive	4(11.42%)	0(0%)	4(5.714%)	
Vomiting				
• Negative	33(94.28%)	34(97.14%)	67(95.71%)	1.000
• Positive	2(5.71%)	1(2.85%)	3(4.28%)	
Itching				
• Negative	35(100%)	35(100%)	70(100%)	1.000
• Positive	0(0%)	0(0%)	0(0%)	
Erytherna				
• Negative	35(100%)	35(100%)	70(100%)	1.000
• Positive	0(0%)	0(0%)	0(0%)	
Respiratory depression				
• Negative	35(100%)	35(100%)	70(100%)	1.000
• Positive	0(0%)	0(0%)	0(0%)	

Nausea and Vomiting were observed in group A patients receiving transdermal fentanyl compared to group B. in group A, 11.42% of the patients had nausea and 5.71% of patients had vomiting whereas in Group B,2.85% of patients had vomiting which was found to be metochlopromide 10 mg intravenously.

DISCUSSION

Although control of postoperative pain is important for recovery, clinical surveys continue to show that many patients experienced moderate to severe degrees of pain following surgery. McCaffery and Ferrell showed that over 50% of surgical patients experienced inadequate pain relief following surgery with negative physiological and psychological consequences.[3]Administration of fentanyl by the transdermal route is appealing because fentanyl is a potent agent with well- defined clinical pharmacological characteristics. Transdermal fentanyl has been demonstrated to provide effective analgesia for acute post operative pain.

Our choice of TDF for postoperative analgesia was to give the patient a source of continuous analgesia so that the need for additional analgesia and nursing observations and care are decreased.The first clinical trials on transdermal fentanyl were performed in patients with acute postoperative pain to prove its analgesic effectiveness in an established pain model and provide data about required dosages, serum concentrations and safety. In most studies, a patch with delivery rate of 50, 75 or 100 µg/h was administered 1 to 8 hours before surgery and removed after 24 or 72 hours. All patients had free access to a rescue medication if pain was not adequately relieved.

Our choice of the transdermal delivery system of fentanyl with a predicted delivery rate of 50 µg/hour was based on a previous study characterizing the relationship between serum

fentanyl concentrations are analgesic effects in patients undergoing abdominal surgery. Some studies demonstrated a non significant reduction in opioid requirements using delivery rates of 25 µg/h .[4]

On the other hand up to 99% of patients were at risk of respiratory depression when being treated with TDF 75 µg/h (administered 8 hours prior to surgery). In our study we applied the patch just before administering spinal anaesthesia. We hypothesized that the TDF will help in relieving the post operative pain by the time spinal analgesia wears off.

Our study and control groups were both comparable demographically. Duration of surgery was comparable between the two groups. In the present study, the mean age in group A was 25.40+3.73 years as against 25.51+3.31 years in group B. this was found to be statistically insignificant (P value = 0.893).

In our study, there was a significant decrease in pain in Group A than compared to Group B which was statistically significant. We are in agreement with Sandler et al's study.**Sandler et al,** in their study found that Transdermal fentanyl 50mcg/hr provided effective analgesia for acute postoperative pain. The VAS pain score were consistently better in the fentanyl group compared with the placebo group, and these lower pain scores were strongly correlated with serum fentanyl concentrations.[5]**Barrera et al,** which assessed the safety and efficacy of transdermal fentanyl used as main postoperative analgesic in patients undergoing dorsal or lumbar spine fusion by comparing the TDF, 50 µg/h, with placebo. VAS scores and rescue analgesic requirements were lower in transdermal fentanyl group ($p<0.05$).[6]

Our study is also consistent with the study done by Samy et al, where pain assessment was done throughout the period of the study (48 hours) by using the VAS score. When comparing the two groups together at the same time, it was found that the VAS was significantly lower in the TDF group compared to the control group.[7]

In the present study, there was a significant difference in the requirement of rescue analgesia. As compared to Group A which received TDF 50mcg/hr. Group B patients required more rescue analgesia with a P value of <0.001. we are in agreement with Sevarino et al and Sandler et al's study. [5,8]**Sevarino et al.** compared TDF in two different delivery rates 25µg/h and 50 µg/h with placebo for postoperative analgesia after abdominal gynecologic surgery (the patches were applied one hour before surgery and removed after 72 hours). They found that there were no differences in the pain intensity in both TDF groups and no differences in rescue analgesia in the TDF group with delivery rate 25 µg/h when compared with the placebo group. There was a significant reduction in the rescue analgesia in the TDF group with a delivery rate of 50 µg/h . [8]

Also Sandler et al. compared TDF in two different delivery rates 50 µg/h and 75 µg/h with placebo for postoperative analgesia after abdominal hysterectomy (the patch was applied two hours before surgery and removed after 72 hours). They found that there were significant reduction in the pain intensity and rescue analgesia in the TDF group with delivery rate of 75 µg/h when compared with the placebo group. But in the TDF group with delivery rate of 50 µg/h there was a significant reduction in rescue analgesic consumption when compared with the placebo group .[5]

In the present study, 11.42% of patients who received TDF 50mcg/hr had nausea and 5.71% of patients had vomiting compared to the control group, where 2.85% of patients had vomiting.**Minville et al. ,** reported that in the TDF group (Duragesic 50 mcg/hr) there were

no reported cases of sedation, respiratory depression or erythema. Pruritus occurred in one patient and nausea / vomiting occurred in 7 patients. The only prominent adverse event was the occurrence of local erythema in 30% of patients received transdermal fentanyl. The transdermal fentanyl group had more pruritus and nausea ($p<0.02$).[9]**In Samy et al** study, Nausea occurred in (33.3%) of patients in the TDF group, which is different from our study where no any case of erythema was reported, and no respiratory depression were observed.[7]

In Sevarino et al study, the TDF group with delivery group rate of 75 µg/h the incidence of respiratory depression, sedation and nausea/vomiting were 11, 22 and 83% respectively [32]. Another study showed that, the incidence of respiratory depression was higher in the TDF group with delivery rate of 75 µg/h (15%) than in the TDF group with delivery rate of 50 µg/h.[8] **Merivirta R et al** reported that a patch delivering fentanyl 12 µg/h did not reduce the need for rescue analgesics or pain score for postoperative pain management.The efficacy of pain medication in hospital was monitored by a nurse who was unaware of the patient's treatment group at 6-hourly intervals between the surgery and the return home. Possible adverse effects, such as somnolence, nausea, itching, and obstipation, as well as breathing frequency, were also monitored using a numerical rating scale. When at home, patients were asked to register their pain scores, their worst pain, analgesic consumption, and adverse effects, using a formulated questionnaire. The patients were interviewed by the investigator during telephone follow-up on the first and/or fourth postoperative day.[10]

Although analgesia (e.g. paracetamol, salicylates, and non-steroidal anti-inflammatory drugs [NSAIDs]) has been recommended as a first-line medication, the risk of gastrointestinal bleeding and renal insufficiency should be taken into account when prescribing NSAIDs. Opioids, such as fentanyl combined with paracetamol, can be administered for patients failing to obtain adequate relief from first-line medications.

However, narcotics have significant side effects, including reduced gastrointestinal motility, urinary retention, reduced respiratory drive, and cognitive deficits with loss of balance, an increase in falls, and depression. Because of the development of those possible side effects, we had to recommend that all patients be admitted to the hospital and use individual fentanyl patches under careful monitoring. Fentanyl patch offers an interesting alternative to oral morphine, and its effectiveness and tolerability were demonstrated by several trials. In general, fentanyl patch has the same adverse effects as other opioids, mainly sedation, nausea, vomiting, and constipation. In comparison with oral morphine, it causes fewer gastrointestinal adverse events. The risk of hypoventilation is comparatively low in patients with cancer. In addition to safety and our experience, the most important reason to choose fentanyl patches instead of other oral opioids was the convenience of changing them every 3 days. Because of a concern for safety, we did not want to increase the dose above 75 µg and the compliance of patients was good.[11]

The TFPs are widely used to control chronic and cancer pain.However investigations about the efficacy of TFPs for acute postoperative pain management have still been reported.They proposed the efficacy of TFPs by showing a comparison of postoperative pain score, the use of rescue analgesics, and the incidence of adverse effects. Those authors demonstrated that postoperative pain control can be achieved with TFPs at dose rates of 12–50 µg/h without severe adverse effect.[12]

In our study, we found the hemodynamic parameters between the two groups were similar and clinically no difference was observed.**Samy et al** found in their study that all cases of the TDF group were hemodynamically stable .[7]**Joseph CC** et al studied, the cumulative morphine consumption progressively increased in the postoperative period from the 4th to the 48th hour (5 ± 3 to 59 ± 30 mg Vs 6 ± 3 to 81 ± 33 mg) respectively in the Fentanyl and the Placebo group, but the difference between the two study groups attained statistical significance at the intervals of 40th (55 ± 29 Vs 70 ± 28 mg; P = 0.04) and 48th (59 ± 32 Vs 81 ± 33 mg; P = 0.01) post operative hours which corresponds to a 21 and 27 percentage reduction of rescue analgesic consumption respectively in the fentanyl group. Considering the comparable intraoperative morphine consumption (5.4 ± 4.5 Vs 4 ± 4.55 mg; P = 0.179), comparably distributed regional anaesthetic cases (TAH cases 14 in F group Vs 20 cases in P group; P = 0.192) and no other systemic analgesics in the postoperative period, the transdermal delivery of fentanyl was attributed to the observation of 27 % reduction of rescue opioid consumption at the end of 48 postoperative hours in the fentanyl group.[13] Similar results were obtained in the present study.

As anyone can expect the 50 μg/hr and 75 μg/hr fentanyl patches would provide more percentage reduction in the rescue analgesic consumption but at the expense of increased incidence of adverse effects.Due to the above reason 50 μg/hr patch was used in present study.Sandler et al demonstrated 36% and 40% reduction in rescue morphine consumption with 50 and 75 μg/hr fentanyl patches respectively over a period of 48 hrs in patients undergoing abdominal hysterectomies. But they observed, that the incidence of nausea vomiting was 57%, oxygen supplementation was required in (30 Vs 62%) and (8 Vs 15%) of patients were withdrawn from the study due to severe respiratory depression respectively in patients who received 50 and 75 μg/hr fentanyl patches. Hence they concluded that the Transdermal Fentanyl Patches should be used only under closed monitored conditions for acute post operative pain with resuscitation facilities close at hand. In present study we observed only nausea and vomiting in 4(11.42%) and 2(5.71%) of patients, none of the patients registered respiratory depression or increased sedation and pruritis.

Joseph CC et al studied, the respiratory depression was commonly associated with the fentanyl concentration more than 1.5 nanogram / ml but the expected maximum plasma concentration Cmax following 25 μg/hr patch is 0.3 to 1.2 nanogram / ml. the difference in the cumulative morphine consumption was not statistically significant in the first 24 postoperative hours. This observation could be because of two reasons one was either the expected maximal plasma concentration Cmax 0.3 to 1.2 nanograms/ml and the subsequent effect site concentration was not attained in the first 24 post operative hours or the attained maximal plasma concentration Cmax was not adequate enough to attenuate nociception and reduce rescue opioid consumption. Though this question can be definitely addressed with the serial plasma concentration studies, considering the time to maximal concentration tmax can vary from 26 to 78 hrs,it may be possible to observe the statistical difference within 24 post operative hours if we would have applied the patch 10 -12 hours before the surgery.[13]

Joseph CC et al studied, 3 hours before the surgery, and the mean surgical duration was 2 ± 0.5 hours, given one hour allowance to complete recovery from anaesthesia, 24 post operative hours coincided with 30 patch hours which was close to the lower range of tmax (26 to 78 hrs). If the patches were applied 10 to 12 hrs before the surgery then the 24 post operative

hours would have coincided with 40 to 42 patch hours which was well within the range of tmax. Significant reduction in the rescue analgesic consumption was demonstrated within 24 post operative hours when 50 μg/hr fentanyl patch was applied 10 hours before the surgery. The median NRS scale at multiple post operative intervals was less than 3, indicating the effective usage of rescue analgesics that is PCA morphine. The hemodynamic fluctuations were within 25% of the base line and correlates to the effective analgesia.[14]In present study also there were no significant side effects with fentanyl at a dosage of 50μg/hr .

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 rst pass metabolism. Many drugs which have a high rst pass metabolism are given through TDS such as Buprenorphine, Clonidine, Estradiol, Fentanyl, Granisetron, Lidocaine, Methylphenidate, Nicotine, Nitroglycerin. TDS allow continuous drug delivery and sustained plasma levels thereby avoiding peaks and turphsin 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. TDS are not extensively used to control postoperative pain due to their slower onset (6-24 hours), unpredictable absorption especially during hypothermia as seen in postoperative period, interpatient variability, high cost, availability of limited number of drugs and physician's familiarity with injectable analgesics. But with newer TDS many of the above problems are attenuated.

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. Overall sedation scores were not increased by transdermal fentanyl. Higher rescue analgesia usage in the placebo and lower rate fentanyl administration groups may account for this. In our study, patients were distinctly informed about the procedure and possible side effects, thus monitoring of each patient was organized in agreement with family member. In very few cases, nausea was reported, especially when patients were moving, which was stopped at moment of siting. Other side effects were not reported

CONCLUSION:

After completing the study, we conclude that transdermal administration of fentanyl 50 μg/h preoperatively is an effective noninvasive and convenient technique for postoperative pain relief after elective caesarian section surgery and allows delivery of a potent analgesic agent with acceptable minimal side effects, better quality of life and better patient acceptability.

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