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Article *in* Minerva chirurgica · December 2014

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Fentanyl transdermal patch (Durogesic® D-TRANS) for post abdominal laparotomy analgesia: a double blind randomized study

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Aim. **The fentanyl transdermal patch (Durogesic®D-TRANS) is a strong pain medication for moderate to severe chronic pain that can provide long-lasting relief for persistent pain. This study was conducted to determine the analgesia and adverse effects of the fentanyl transdermal patch (Durogesic®D-TRANS) postelective laparotomy.**

Methods. **One-hundred twenty patients undergoing elective laparotomy were randomized into two groups of fentanyl and placebo. In the first group, patients received two fentanyl patches with 25 and 50 µg in 10 hours preoperatively. Patient's postoperative assessments included pain score, adverse effects, mean amount and interval of supplementary morphine, respiratory rate and oxygen saturation, which were recorded during 36 hours.**

Results. **The mean pain intensity scores over 36 hours in fentanyl transdermal patch durogesic (FTD) group were significantly less than placebo group (FTD, 35.28; placebo, 46.61 and P=0.01). However, the pain score at the 3rd timepoint in the placebo group was slightly less than the FTD group (39.4±2.23 *vs.* 39.47±4.97, respectively). The mean interval and amount of supplementary morphine were significantly better in the FTD group than the placebo group (FTD 367.7±349.7 min vs. placebo 59±13.88 min; P=0.04 and FTD 2.10±3.46 mg vs. 29.15±3.71 mg; P < 0.001, respectively). The incidence of adverse effects including vomiting (FTD 16 *vs.* placebo 9; P=0.45), nausea (FTD 22 *vs.* placebo 18; P=0.33), itching (FTD 16 *vs.* placebo 18; P=1.00) and respiratory depression (FTD 1 *vs.* placebo 0; P=1.00) were not significant between the groups, except the dizziness that had a higher incidence in the FTD group (FTD 23 *vs.* placebo 1; P=0.02).**

Conclusion. **It seems that the fentanyl transdermal patch system is a safe and effective procedure to use in post laparotomy analgesia and its related adverse effects are not serious.**

KEY WORDS: Transdermal patch - Laparotomy - Analgesia - Placebos - Postoperative period.

Despite the constantly increasing understanding of pain mechanisms and improved technology in pain therapy for the anesthetist, the management of postoperative pain continues to remain problematic and unsatisfactory.[1] A lot of surveys over a long time show that the majority of patients still suffer from moderate to severe postoperative pain.[2] If pain is not adequately managed, it will have devastating effects on the quality of life of the patients such as prolong recovery,

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depression and even loss of employment.[3] Nowadays, pain management in addition to a medical view was approved as a human right and must be provided by governments for patients. The importance of adequately managing postoperative pain is highlighted by a number of policies developed by both professional and governmental bodies to detect and manage this condition.[4, 5]

The transdermal system (epidural) is used to pain relief and management of most conditions. This management system is a simple, useful, inexpensive preprogrammed routine procedure for postoperative analgesia, without disadvantages of the Intravenous method such as analgesic gaps or drug addiction.[6] Fentanyl with specific kinetics and chemical properties is introduced as one of the most commonly used drug for postoperative pain management, which can be given as oral, IV and epidural with high potency.[7, 8] This medication was originally approved by the FDA, and is a synthetic narcotic that is 1000 times more potent than morphine and can reduce the pain perception remarkably.[9] Four transdermal patches of fentanyl based on the skin covering area are available. It seems that in the transdermal method after 8-12 h its blood concentration achieved is about IV method, and remains constant over the 72 h till the patch is worn.[10] Results of various studies have shown that the fentanyl effectiveness depend various factors such as the ability of drug absorption and depletion.[11]

Patients who undergo the laparotomy need pain relief postoperatively. It has been reported that pain with different intensity is expected in laparotomy depending on the demographics characteristics of patients, surgery area and skill of the surgeon.[12] The main objectives of this study were to evaluate the efficacy, competence and safeness of the fentanyl transdermal patches for post laparotomy pain management or analgesia.

Materials and methods

This double blind randomized, placebo-controlled study was conducted from September 2011 to June 2013 among 120 adults who underwent general anesthesia for exploratory laparotomy and were expected to have moderate to severe pain requiring epidural opioids for at least 36 hours after surgery. Eligible patients were ASA physical status I and II. The patient's mean and age range were 44±4.6 and 25 to 65 years, respectively. In addition, their weight range was between 40 and 90 kg, with a mean weight of 63±55 kg. The patients by random number Tables were assigned to one of two groups depended on the used pain relief method, a fentanyl transdermal patch system (N.=60) group (Duragestic 25 and 50 µg/h Matrix Fentanyl Patch, Janssen Pharmaceutica N.V., Belgium) and placebo (N.=60) group. Excluded were patients with history of morphine or other drug addictions, depression or other affective disorders, sensitivity to morphine or fentanyl and retention of CO_2, active skin disease, and poor mental condition. All participants have been informed that, they can withdraw from the study at any stage and for any reason. From all participants a written informed consent was obtained and the study was authorized by the Medical and Biological Research Ethics Committee of Shahid Sadoughi University of Medical Sciences and Health Services, Yazd.

The pain assessment was done by a 100 mm ungraded visual analog scale (VAS) the pain status of participants at the time of hospital admission based on the VAS was at I and II. The placebo patches were identical to the fentanyl transdermal system except that the patches had no fentanyl. Based on body weight, two fentanyl patches (25 µg patches for patients with 40-60 kg and 50 µg patches for patients with 60-90 kg weight) were applied 10 h preoperatively to the spine of patients, near to the scapula. Anesthesia was given as per standard protocol. In summary, 30 min before laparotomy, all patients received Midazolam 0.03 mg/kg IV. Then, 4-6 min before the surgical incision fentanyl 2 µg/kg IV, as an anesthesia induction agent was administered, and subsequently thiopental sodium and atracurium were injected in 5 µg/kg and 0.06 µg/

kg doses, respectively. To prevent pain, fentanyl 1 µg/kg IV, was administrated every 30 min and patient's anesthesia status was monitored with a mixed oxygen and nitrous oxide with 1:1 ratio. The patients were ventilated using a semi-closed system to maintain CO_2 value 34 to 36 mm Hg. One patient due to the respiratory rhythm complication (>8 per min) or for not responding to oxygen therapy were treated with naloxone and then were excluded from the study.

Moreover, in case of hypotension, nausea or vomiting patients were treated by fluid therapy and 10 mg metoclopramide. After the operation, patients were transferred to post-anesthesia care unit (PACU), and during recovery for the postoperative pain assessments, a 100 mm ungraded Visual Analog Scale (VAS) at 0, 1, 3, 6, 18, 24 and 36 hours post operation intervals was used, thereafter until 36 h the postoperative analgesia was supplied using 5 mg IV morphine. In addition, the clinical data such as pain intensity at specific timepoints, time and the amount of first postoperative urgent requested morphine until 36 hours and adverse effects were documented. In order to eliminate the risk of bias, all surgeries were operated only by a skilled surgeon (by second author). All of the operations were exploratory laparotomy for diagnostic evaluation of abdominal chronic pain.

Statistical analysis

Demographic and clinical variables were summarized according to treatment group for all randomized patients. Student t-test (two tailed, independent) and Fisher Exact/Mann-Whitney, and Wilcoxon test were used to find the significance of study parameters on continuous and categorical scales between treatment groups, respectively. Statistical significance was set at $P<0.05$. SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) was used in the analyses.

Results

Demographic characteristics of the randomized patients are shown in Table I. This study was initiated totally with 120 patients, but 119 patients were eligible to continue, 1 case from FTD group due to the intense respiratory depression was withdrawal from the study. The mean age and S±D of the FTD and the placebo groups was 50.31±6.4 and 52.05±6.1 years, respectively. Female patients were slightly predominant but was not significant (female 52.5% *vs.* males 47.5%; P=1.00). Most of the patients were ASA physical status II (ASA I 43 *vs.* ASA II 76; P=0.74). Mean duration of the operations and anesthesia were not significantly different between FTD and placebo groups (FTD 73.26±10.38 min *vs.* placebo 74.9±14.5 min; P=0.68 for operation and FTD 84.15±10.58 min *vs.* placebo 87.45±13.6 min; P=0.41 for anesthesia).

The clinical findings about the patients are shown in Table II.The mean pain intensity score was significantly less for patients in the FTD group than for patients in the

TABLE I.—*Patient demographic characteristics.*

Variables	FTD (N.=60)	Control (N.=60)	P-value
Age (yr)	50.31±6.4	52.05±6.1	0.39
Gender			
Male	29(48.4)	28(46.6)	1.00
Female	31(51.6)	32(53.3)	
Weight (kg)	68.15±11.80	65.95±9.85	0.52
Height (cm)	161.26±7.92	163.45±7.53	0.38
ASA			
ASA I	20(33.4)	24(40.0)	0.74
ASA II	40(66.6)	36(60.0)	
Duration of operation (min)	73.26±10.38	74.9±14.5	0.68
Duration of anesthesia (min)	84.15±10.85	87.45±13.6	0.41

TABLE II.—*Clinical variables of the randomized patients.*

Variables	FTD group (N.=60)	Placebo group (N.=60)	P-values
Respiratory rate	15.05±1.58	16.45±3.11	0.69
Heartbeat	79.05±5.2	70.2±7.73	0.86
Pain scores	35.28±4.29	46.61±4.38	0.01
Arterial oxygen saturation (SaO_2)	95.42±1.07	95.75±1.33	0.10
Arterial blood pressure	95±6.87	95.33±5.45	0.19
Diastolic blood pressure	70.78±6.72	82.25±4.12	0.06
Systolic blood pressure	123.42±11.06	121.5±12.25	0.44

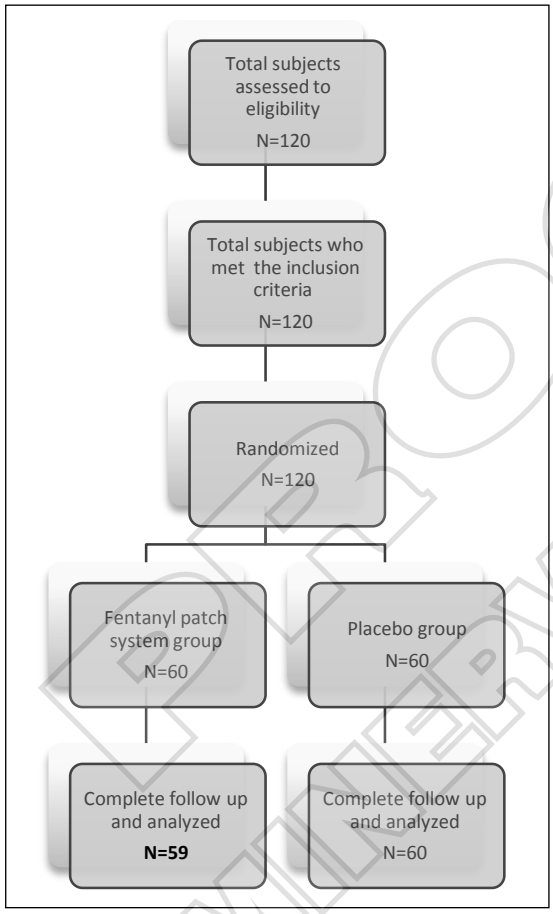

Figure 1.—CONSORT flow diagram.

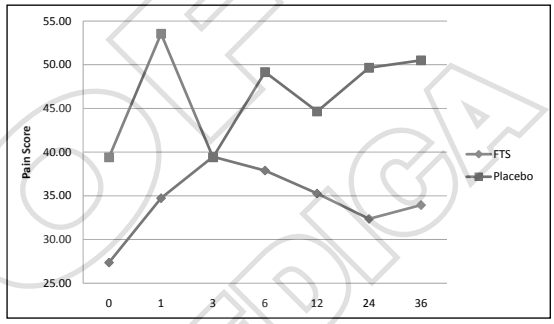

Figure 2.—Pain scores between FTD and Placebo groups at different moments.

placebo group over 36 h in the PACU (FTD 35.28±4.29 *vs.* placebo 46.61±4.38; P=0.01). Similarly significant differences of pain intensity scores were found between groups at each measured timepoints (0, 1,6,12, 24 and 36), except at 3rd timepoint [Figure 2], which in this timepoint it was slightly less in the placebo group in comparison with the TDF group (FTD 39.47±4.97 *vs.* placebo 39.4±2.23). The pre and post laparotomy heart rate and systolic, diastolic and arterial blood pressure were determined for both groups, but there were not significant differences (P=0.86, P=0.44, P=0.06 and P=0.10, respectively).

The findings about supplementary morphine are shown in Table III. The mean interval of supplementary morphine postoperatively for the FTD group was significantly greater than placebo group (FTD 367.7±349.7 min *vs.* placebo 59±13.88; P=0.04). The mean amount of the supplementary requested morphine over 36 h was significantly less in the FTD group than placebo group (FTD 2.10±3.46 mg *vs.* placebo 29.15±3.71 mg; P<0.001).

The incidences of adverse effects between the groups are shown in Table IV. The incidences of adverse effects including nausea, vomiting, itching and respiratory depression was approximately similar between groups. However, the incidence of dizziness was significantly greater in FTD group (FTD 38.3% *vs.* placebo 1.6%; P=0.02).

TABLE III.—*The mean interval and amount of supplementary morphine.*

Mean of sup morphine	TDF	Placebo	p-value
Mean interval of first sup. morphine (min)	367.7±349.7	59±13.88	0.04
Mean amount of sup morphine (mg)	2.10±3.46	29.15±3.71	< 0.001

TABLE IV.—*Incidences of adverse effects between FTD and placebo groups.*

Side effect	TDF (%)	Placebo (%)	P-value
Dizziness	23(38.3)	1(1.6)	0.02
Nausea	22(36.6)	18(30.0)	0.33
Vomiting	16(26.6)	9(15.0)	0.45
Itching	16(26.6)	18(30.0)	1.00
Respiratory depression	1(1.7)	0(0.00)	0.10

Discussion

Fentanyl is an opioid analgesic that binds to specific receptors at many sites within the CNS resulting in increased pain threshold, altered pain reception and inhibition of ascending pain pathways.[13] Its patch system is one of the greatest commercial successes in transdermal drug delivery. The suitability of this molecule for delivery through skin had been identified in the 1970s, and subsequently, a number of transdermal formulations became available on the market.[14]

In the present study there was no significant difference between patient's gender, age, weight, height, duration of surgery and anesthesia between the FTD and placebo groups. Also no significant difference was found in the physical status of patients. There were significant differences in the VAS scores between groups. Thus, the analgesic effects of fentanyl administered by patch systems were effective and different from placebo patches. Also the presence of a significant difference in the amount of excessive required morphine between the groups over 36 hours (from patient recovery timepoints to first excessive morphine required) in this study, which highlighted that FTD system had better effectiveness.

This study had a major difference with other studies, in which the fentanyl transdermal patches were applied 10 h preoperatively compared to 2 hours in most other studies.[15] It seems that the plasma concentration of the fentanyl reaches to the highest level at this interval. So, immediately after the surgery patients will experience severe pain, but due to the effects of the fentanyl, patients did not suffer considerable pain. Also their need for supplementary morphine decreased compared to the controls. Furthermore, due to the type of surgery with peritoneal irritation, fentanyl patches were removed 36 hours after surgery. According to the pharmacokinetic data of FTD demonstrating a half life of ca 72 hours, an adequate effect is anticipated to last as late as the third day postoperatively.

In this study which the fentanyl patches were applied 10 h preoperatively, the mean of excessive required morphine, throughout 36 hours, in the placebo group was significantly higher than FTD group (29.15±3.7 *vs.* 2.10±; P<0.001). In addition, the mean of interval between end of the operations and first excessive morphine administration in the PACU in the placebo group was less compared to the FTD group (FTD 59±13.8 min *vs.* placebo 367.7±349.7 min; P=0.04). Similarly, Sandler *et al.*,[2] have reported high amounts of required morphine in PACU + ward for placebo compared to other groups (TTSF-75 56.7±7.9 mg, TTSF-50 61.2±6.7 mg, placebo 94.4±7.7 mg). The main reason for the differences in the mean of required morphine in Sandler *et al.*, study with the present study due to the time of the patch application (2 hours *vs.* 10 hours) and follow-up period (36 hours *vs.* 72 hours).

There are several studies that reported results similar to our finding in the present study about lower opioid administration in fentanyl groups.[16-18] But, in a study by Geoffrey *et al.* in 1990, there was no significant difference in the amount of supplementary pethidine required by the fentanyl and placebo groups over the entire 0-48 hours time period.[19] This difference with obtained results in the last study may reflect the longer duration of pain relief associated with pethidine compared to fentanyl administered intraoperatively. It is also consistent with the attainment of sufficient blood fentanyl concentrations for the control of postoperative pain after an initial delay. Minville *et al.* studied the use of morphine, fentanyl 48 hours after surgery in groups of 8 mg and 67 mg, respectively.[20] These differences may be arisen due to the type of surgeries and postoperative duration. Also in their study titrated morphine in the PACU and in the ward PCA were used for analgesia.

The most common opioids related adverse effects are nausea, vomiting, headache, and erythema, with low rates of respiratory depression. However, postoperative nausea and vomiting (PONV) are frequently caused by opioids, but the aetiology of PONV is multifactorial.[21] PONV occurs in 25% to 30% of surgeries and significantly contributes to patients' discomfort, distress, and dissatisfaction.[22] In the systematic review by Tramèr and Walder, the incidence of nausea and vomiting after various kinds of operations in patients receiving no prophylactic antiemetic treatment added to their PCA morphine was approximately 50%. Increasing doses lead to respiratory impairment, corresponding to plasma concentrations above 1.4–2.5 ng/mL. Excessive use and abuse of iontophoretic fentanyl can lead to death.[23] The adverse effects that were recorded in this study in the FTD group included those of common post-operative opioid-related adverse effects; included vomiting, nausea and constipation. However none of these effects were so much serious and were resolved in a short time. Most adverse effects with mild or moderate severity are commonly experienced by patients receiving opioid analgesia and by patients in the immediate postoperative period.[24] In our study there was not statistically significant difference between the groups in the number of patients who nauseated or vomited.

The fentanyl transdermal system (patch) is strong medicine for management of persistent, moderate to severe chronic pain in opioid-tolerant patients. The fentanyl patch should only be used when other less potent medicines have not been effective and when pain needs to be controlled around the clock.[13, 14] Fentanyl patches may cause serious or life-threatening breathing problems, especially during the first 72 hours. Therefore, patients should be informed about the risks.[24]

Postoperative respiratory failure (PRF) is the most serious postoperative pulmonary complication.[25] It has been reported that 9% to 40% of the patients who undergo abdominal surgery experience postoperative pulmonary complications.[26] Many factors can change both the magnitude and duration of respiratory depression after opioid administration. In the present study 1.7% (N.=1) of patients in FTD group were withdraw due to the adverse respiratory effects during surgery, after patch removal and naloxone rescue. Also, in 25.5% of TDF group, O_2 saturation was seen less than was seen 90% who were treated in the PACU with nasal O_2. In the placebo group, one patient had low PaO_2 values less than 90% but had no need for respiratory support. Bloom *et al.* estimated the burden of postoperative respiratory depression and sedation following 894076 abdominal surgeries.[27] They reported 30244 (3.7%) cases of naloxone rescue in the cohort study with significant hospital mortality between naloxone and Nonnaloxone groups ($P<0.001$). The study results had shown that postoperative naloxone rescue following paraenteral opioids after abdominal surgery is surprisingly common (3.7%) and is associated with significant increases in mortality, hospital length of stay, resource use, and use of ventilatory support. There are several reports showing that Fentanyl cause delayed respi-

ratory depression in the post-operative period. In one of the studies, it was reported a sudden onset of extreme abdominal and thoracic rigidity, leading to respiratory depression in 15 patients, 2-6 hours after the last dose of fentanyl after an apparently normal recovery from anaesthesia, which was rapidly reversed with naloxone (28). Adams and Pybus have shown delayed respiratory depression caused by to fentanyl up to 4 h after the surgery in the postoperative period.[29] Sandler *et al.* used fentanyl transdermal patches as analgesia among patients undergoing abdominal hysterectomy. They reported that in 11% patients of TDF group due respiratory depression the patches were removed and in 8% naloxone rescue were administrated. They deduced that despite adequate relief of pain by fentanyl respiratory depression is possible in some cases.[2] Therefore, it seems respiratory depression and need for naloxone rescue among patients with abdominal surgery and presumably in the laparotomy cases are frequent effects.

Conclusions

Application of transdermal fentanyl patches 10 hours preoperatively is associated with moderate supplementary opioid requirements for analgesia in the early postoperative period and ongoing opioid supplementation for at least 72 hours, without additive side effects in patients undergoing abdominal laparotomy.

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Funding.—This research was supported, in part, by Grant no. 131/821 from Shahid Sadoughi University of Medical Sciences. The authors would like to thank the General Surgery ward of Shahid Sadoughi training hospital for providing the opportunity and impetus to perform this study.

Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Received on July 8, 2014.
Accepted for publication on December 14, 2014.