Efficacy and Safety of Transdermal Fentanyl Patches on Postoperative Pain Relief after Major Abdominal Surgery

Samy A. Amr, Mostafa G. Mostafa, and Mohamed A.M. Mostafa

Department of Anesthesia, ICU & Pain Management, South Egypt Cancer Institute, Assiut University, Egypt.
saaerfan62@yahoo.com.ph

Abstract: A double blind study was carried out on 100 adult ASA grade I/II patients to evaluate efficacy and safety of transdermal fentanyl for postoperative pain relief. Patients were randomly divided into 2 groups, group I (n=50) each patient received transdermal therapeutic system-fentanyl 50µg/h [TDF group], and group II (n=50) each patient received transdermal placebo patch [C group]. All patches were placed 10 hours preoperatively and covered with adhesive plaster to confirm fixation and to blind the anesthetists and observers for the type of the used patches. Surgery were done under general anesthesia and i.v. morphine were given once patients start to first experienced pain postoperatively. The two groups did not differ significantly as regard age, weights, sex, duration of surgery or anesthesia and hemodynamic parameters throughout the period of the study (48 hours). Pain intensity was lower in TDF group than C group in the immediate postoperative period and at 12^{th} to 48^{th} hours. Percentage of patients with normal postoperative O_2 saturation were higher in TDF group than C group (P<0.000), in both groups no patient suffered from severe hypoxia (O_2 saturation < 90%). First time of i.v. morphine administration was short in C group as compared to TDF group, (0.7±0.3hour Vs 1.7±5.8hour, *P*=0.003). Frequency and total morphine consumption were significantly higher in C group than TDF group (*P*<0.000). Intraoperative fentanyl consumption was also higher in C group (250.3±35.7) as compared with TDF group (118.2±19.1). Nausea and vomiting were lower in TDF group (32%) than C group (62%),(*P*<0.05), and no other side effects were observed in the two groups. Conclusion: Transdermal fentanyl patch 50µg/h is an effective non invasive and can be used safely for postoperative pain relief in major abdominal surgery with minimal acceptable side effects.
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1. Introduction:

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 **[1]**. McCaffery and Ferrell showed that over 50% of surgical patients experienced inadequate pain relief following surgery with negative physiological and psychological consequences **[2]**.

In recent years, increased interest in the treatment of acute and chronic pain has resulted in the development of transdermal delivery systems for analgesia. Transdermal drug delivery offers the potential benefits of simplicity, efficacy, and patient acceptance. In theory, a transdermal delivery system can provide a stable serum concentration for an extended period of time with acceptable interpatients variability. The physicochemical and physiological principles governing transdermal drug absorption have previously been describe **[3,4]**. Administration of fentanyl by the transdermal route is appealing because fentanyl is a potent agent with well-defined clinical pharmacological characteristics **[5]**. Transdermal delivery system for fentanyl has been developed and approved for the treatment of chronic pain, and it has been demonstrated that transdermal fentanyl provides effective analgesia for acute postoperative pain **[6]**.

The use of continuous opioid administration versus PCA in managing postoperative pain is dependent on a variety of factors, and may be especially useful in subsets of patients who cannot use PCA, such as elderly, disoriented, or handicapped patients. Also when comparing the TDF with the PCA it has several advantages: first, it costs less than PCA, because PCA is expensive, it may not be available to every patient; therefore, TDF could be an interesting alternative. Moreover, TDF does not require i.v. access. The risk of infection is decreased, and the patient's comfort improved. In addition, TDF does not need to be programmed, so avoiding program errors that occur with PCA. At the same time the skin is an organic system with a large surface area and its use as a route of drug administration should be considered when evaluating patients, particularly if they meet any of the above criteria **[6].**

The early transdermal administration of fentanyl was achieved via a reservoir patch **[7]**. However, this patch was associated with significant

interindividual variability, so fentanyl matrix patch was developed and designed to be bioequivalent to the original reservoir patch with a constant and reliable fentanyl release. However, comparing it with the reservoir patch, the fentanyl in the matrix patch is entirely dissolved in the adhesive, thus opioid dissolution is not required prior to its diffusion through the matrix following application **[7]**. The matrix patch also has better flexibility and skin conformability, and produce linear fentanyl dose kinetics with negligible dose loading **[7,8]**.

Taylor and Stanbury [9] have been suggested that the way for improving postoperative pain management should includes procedure specific guidelines, new methods to predict postoperative pain and new drugs and delivery systems. So our aim in this study was to evaluate the effectiveness and safety of transdermal fentanyl patches for relieving postoperative pain after major abdominal surgery under general anesthesia.

2.Patients and Methods:

After Hospital Ethics Committee approval, the study was conducted on 100 patients after obtaining their written informed consent, their age were between 20-60 years, ASA I/II with body weight ranged between 65kg and 100 kg. They were scheduled to undergo major pelvi-abdominal cancer surgery under general anesthesia. This study was carried out in South Egypt Cancer Institute from October 2009 to August 2011. We exclude, patients received preoperative opioids, having contraindication to regional block (coagulation defect, local infection at the site of injection or patient refusal), patients having moderate or severe renal and hepatic impairment, patients with documented history of opioid sensitivity or drug abuse.

All patients were randomly allocated to one of the following groups: **Group I,** Patients were received Transdermal Therapeutic System-Fentanyl (TDF group, n=50) 50 µg / h patch, placed 10 hours preoperatively and **Group II**, Patients were received transdermal placebo patch, placed 10 hours preoperatively (C group, n=50).

Before any patch placement a preoperative visit was done to all patients to assess patient fitness for operation, to alleviate anxiety and to make them familiarized with the VAS. Patients also were informed about transdermal patches (its efficacy in the treatment of postoperative pain and its possible side effects) and they informed about method of application. The patients were also assured that they would receive i.v. morphine once they start to first experienced pain postoperatively.

In both groups general anesthesia was induced using lidocaine (1.5mg/kg), propofol (1-2 mg/kg), cisatracurium (0.15 mg/kg) to facilitate intubation and small dose of fentanyl (1µg/kg to avoid stress of intubation) and maintained using inhalational anesthetic (sevoflurane 2-3%) and muscle relaxant (cisatracurium 0.03mg/kg) with mechanical ventilation at rate of 10 breaths/minute and tidal volume of 10ml/kg with oxygen flow of 2 liters/minute. Increments of fentanyl were allowed until 30 minutes prior to skin closure to maintain cardiovascular status (HR and BP) at 20% around the preoperative status.

At the end of operation residual muscle relaxation was reversed using neostigmine (0.05mg/kg) and atropine [0.02mg/kg (0.2mg for each 0.5mg of neostigmine)]. Intraoperative monitoring included ECG, pulse oximetry, NIBP, $ETCO_2$ and invasive blood pressure (if needed for the operation). In the recovery room, if patients of the studied groups were awake, breath spontaneously and be able to answer questions and follow command were shifted to PACU for observation and follow up for at least 48 hours (the period of the study). Any patient with surgical problems and needs any surgical interference after recovery or who unable to communicate postoperatively were excluded from the study.

In our study we used fentanyl patches [Durogesic® D-Trans® (matrix) from Janssen-Cilag] with delivery rate of 50µg/h patch. Either fentanyl patches or placebo patches were placed on a hair-free area (the antero-lateral chest wall) and mounted in place and covered by adhesive plaster. The area was not shaved to maintain the integrity of the skin to maintain normal absorption (if necessary hair was only clipped from the patch site prior to application). The patch was removed 48 hours postoperatively. The patients were told that the patch would relieve their postoperative pain. All patients were monitored during the preoperative period for complications such as nausea, vomiting, respiratory depression, hemodynamic instability and sedation.

As soon as patients were oriented and when patients first experienced pain or in case of insufficient analgesia (pain score > 3) the patients were administered intermittent doses of i.v. morphine (5-10 mg) through the subsequent 90 minutes period and until the end of the study period (48 hours).

Monitoring and assessment:

Each patient in both groups were followed up immediately postoperative for 90 minutes and every four hours for 48 hours postoperatively and were monitored for, the hemodynamic parameters (heart rate, ECG and noninvasive blood pressure),

respiratory pattern in the form of respiratory rate, oxygen saturation (using pulse oximetry) and end tidal CO_2. The duration of analgesia, as indicated by the onset of pain, pain intensity score by using the VAS, (which is a line graded from 0-10, where 0 = no pain and 10 = the worst pain imaginable) was performed in the immediate postoperative period and at 30, 60 and 90 minutes then every 4 hours for 48 hours. [Patients who had pain score > 3 received an additional dose of intravenous morphine (5-10 mg)]. Also side effects of opioids such as nausea and vomiting, itching. respiratory depression, and erythema were recorded. Sedation by Ramsay sedation score (1-5) where: 1 = Awake, 2 = drowsy, 3 = Sleepy but rousable to mild stimulation, 4 = Sleepy but rousable to strong stimulation, 5 = Unconscious patient not answering to contact, were also recorded.

The doses of fentanyl consumed during the operation, first time of requesting analgesia, frequency of morphine administration and the total dose of morphine consumed by the patient during the period of the study were recorded in all groups. Medical management of respiratory depression consisted of removal of the offended drug (removal of the patch) and administration of i.v. incremental doses of naloxone (80-100 µg) according to patient response. All the observations were done and recorded by another anesthetist not involved or unaware for patients group assignment.

Statistical analysis:

Data were analyzed by using SPSS version 15 (Chicago, USA). Data were expressed as mean ±SD or number (%). Age, weight, duration of surgery or anesthesia and analgesic consumption compared using unpaired t-test. Percentage and frequencies of patients compared using Chi-square. Repeated measures ANOVA was used to compare the other variables. A *P*-value ≤ 0.05 was considered statistically significant.

3. Results

Fifty patients in each group completed the study with no significant differences between the two groups with respect to demographic variables (age, sex, body weight). Duration of surgery and anesthesia were also comparable between the two groups. There were no patient withdrawals due to severe adverse events, table (1).

Pain intensity score was compared by using the VAS score in the first 90 minutes and it was found that, there were no patients in the TDF group showed pain score more than 7cm. But 15% of patients in group C had score more than 7cm (***P*** < 0.001). Also 14 % and 25% of patients in group TDF and group C respectively had score between 5-7cm (***P*** < 0.001), 24% and 35% of patients in group TDF and group C respectively had score between 3-5cm (***P*** < 0.001), and 62 % and 25% of patients in group TDF and group C respectively had score less than 3cm (***P*** < 0.001), table (2).

Pain assessment was done throughout the period of the study (48 hours) by using VAS score. When comparing the two groups together at the same time (by using ANOVA test), it was found that the VAS was significantly lower in the TDF group during the immediate postoperative period and from the 12th to the 48th hour as compared with the C group (***P***<0.001). But from the 4th to 8th hour, there was no significant difference between the two groups, Fig I.

Table (1): Patient characteristics, duration of surgery and anesthesia.

	TDF group (n= 50)	C group (n= 50)
Sex: No. (%)		
Male	23 (46%)	24 (48%)
Female	27 (54%)	26 (52%)
Age: (years)		
Mean ± SD	46.9 ± 8.1	48.5 ± 10.0
Weight: (kg)		
Mean ± SD	74.3 ± 7.6	76.8 ± 6.1
Duration of surgery (min)	185.6 ±25.4	182.5 ±27.8
Duration of anesthesia (min)	212.5 ±30.4	215.8 ±32.6

Table (2): Distribution of pain intensity score in the first 90 minutes.

Pain score	TDF	C	*P* value
< 3 cm	62 %	25%	0.000*
3-5 cm	24%	35%	0.000*
5-7 cm	14 %	25%	0.000*
> 7 cm	0.0%	15%	0.000*

***P**: TDF versus C

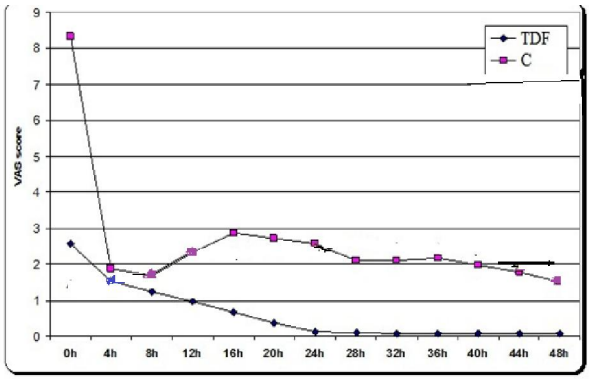

Fig (I): VAS score.

There were no statistically significant differences between the two groups in the hemodynamic parameters [systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) throughout the period of the study.

The percentage of patients with normal saturation on room air was significantly higher in TDF group than in the C group (***P*** < 0.001). Also the percentage of patients with mild hypoxia was significantly lower in the TDF group than in the C group (***P*** < 0.001). In both groups no patients suffered from severe postoperative hypoxia (Table 3). The first time of morphine administration in group C was shorter than group TDF (*P*<0.01). There were significant differences between the two groups as regard to frequency of morphine administration, the TDF group had a lower frequency of administration of morphine as compared to C group (0.5 ± 0.73 Vs 4.8 ± 0.85) (***P*** < 0.001).

In the TDF group patients consumed less amount of morphine than the C group, 2.5 ± 3.65 mg Vs 29.00 ± 4.23 mg. Also intraoperative fentanyl consumption was higher in the C group as compared to the TDF group (250.3 ± 35.7 µg Vs 118.2 ± 19.1 µg) (*P*< 0.001), table (4).

The adverse effects were compared in the two groups throughout the period of the study. It was found that, there was statistically significant difference in nausea & vomiting, the TDF group had a lower incidence of nausea and vomiting (16 (32%) cases) versus (31(62%) cases) for the C group (***P*** < 0.05). Nausea and vomiting were treated by giving dexamethasone 8mg and metoclopromide 10 mg intravenously.

. There were no reported cases of itching or respiratory depression in TDF group and C group. There were also no reported cases of erythema at the sites of patch application. The overall sedation score was significantly higher in C group (2.46±1.9) as compared to TDF group (1.45±0.6), table (5).

Table (3): Percentage of patients with normal saturation, mild hypoxia and severe hypoxia (during 48 hours).

Oxygen saturation	TDF	C	*P* value
Normal saturation (95%-100%)	87 %	80.0%	0.000*
Mild hypoxia (90%-94%)	12 %	20.0%	0.000*
Severe hypoxia (<90%)	0.0%	0.0%	1.000

***P :** TDF versus C

Table (4): Morphine and fentanyl consumption (mean ± SD).

Group	TDF	C	*P* value
First time of morphine administration (h)	1.7 ± 5.8	0.7 ± 0.3	0.003*
Frequency of morphine administration.	0.5 ± 0.73	4.8 ± 0.85	0.000*
Total dose of morphine consumption (mg)	2.5 ± 3.65	29.00 ± 4.23	0.000*
Intraoperative fentanyl consumption (µg)	118.2 ± 19.1	250.3 ± 35.7	0.000*

**P*: TDF versus C

Table (5): Adverse effects.

Adverse effects	TDF	C	P value
Itching	0.0%	0.0%	1.000
Nausea and vomiting	16(32 %)	31(62 %)	0.020*
Erythema	0.0%	0.0%	1.000
Respiratory depression	0.0%	0.0%	1.000
Sedation score (mean±SD)	1.45±0.6	2.46±1.9	0.000*

***P*:** TDF versus C

4. Discussion

Central sensitization and hyper excitability develop after the surgical incision and result in amplification of postoperative pain. Preventing the establishment of altered central processing by analgesic treatment may result in short-term (e.g., reduction in postoperative pain and accelerated recovery) and long-term (e.g., reduction in chronic pain and improvement in health related quality of life) benefits during a patient's convalescence **[10]**.

Our choice of TDF for postoperative analgesia was to give the patient a source of continuous analgesia so that his need for additional analgesia and nursing are decreased. This is because some studies of nursing behavior, concluded that nurses tended to doubt what patients say about their pain, often do not ask about pain and overestimate the percentage of patients who over-report their pain. Also another studies were, cleared that nurses do not always administer all available analgesia despite patients being in pain **[11-15]**.

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 a delivery rate of 50, 75 or 100µg/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 **[16]**.

There were several case reports in which the TDF was used for the management of acute pain and resulted in fatal complications. Some of these cases include, one patient 19-year-old woman with acute abdominal pain, TDF was started with a dose of 100 µg/h, she died at home from respiratory depression **[17]**.

Another case was reported by **Flannagan *et al.* [18]** in which a 31-years old man died from fentanyl poisoning after he apparently obtained fentanyl from a used patch removed from a diseased patient. The man had no other known access to this drug. The exact route of administration (e.g. injection or transmucosal administration of patch content) was not known. Another case reported by **Hardwick *et al.* [19],** in which a 17-year-old male treated with TDF after a wisdom tooth extraction was found dead after going to sleep on a heated waterbed.

Another case reported by **Edinboro *et al.* [20],** in which an 83- year-old female with terminal cancer was found dead with three 100µg/h fentanyl patches; death was caused by fentanyl overdose, but it was not established if this was an accidental overdose, a suicide or possibly a homicide. Another case reported, in which a 31-year-old man died from fentanyl overdose via mucous membrane absorption. At intubation, a fentanyl patch (75µg/h) was removed from the buccal cavity, but it was documented that patients to whom the TDF was applied require monitoring like other parentral routes for opioid administration **[21,22]**.

Our study demonstrated that continuous opioid administration using transdermal delivery of fentanyl with a predicted nominal delivery rate of 50ug/hour achieves effective and safe postoperative analgesia in patients undergoing pelvi-abdominal oncologic surgery. This is in contrast to what was reported previously in which continuous opioid infusions (via transdermal fentanyl) plus PCA resulted in increased side effects with no increase in analgesia versus PCA alone **[23,24]**. Also Sevarino et al, have been questioned the utility of transdermal fentanyl in combination with i.v. morphine for postoperative orthopedic pain **[25]**.

Hug[26], was reported that although the therapeutic range for serum fentanyl concentration has been reported as 1–3ng/ml, there is wide interpatients variability, resulting from pharmacokinetic, pharmacodynamic and psychological factors.

Our choice of the transdermal delivery system of fentanyl with a predicted delivery rate of 50µg/hour was based on a previous study characterizing the relationship between serum fentanyl concentrations and analgesic effects in patients undergoing abdominal surgery. Some studies demonstrated a non significant reduction in opioid requirements using delivery rates of 25µg/h **[27-29].** On the other hand, up to 9% of patients were at risk of respiratory depression when being treated with TDF 75µg/h (administered 8 hours prior to surgery) **[30]**. For management of postoperative pain, it may be desirable to apply transdermal fentanyl several hours before completion of surgery so that MEC can be achieved prior to or concomitant with the end of surgery. Additionally, the slow decline in serum fentanyl levels offers the potential advantage that the transition to other forms of pain management can be accomplished without an abrupt loss of analgesia. However, if prompt and complete termination of opioid effect is desired, serial injections of an opioid antagonist such as naloxone may be required until the skin depot is sufficiently depleted **[6]**.

When serum fentanyl concentrations reached a plateau approximately 14 hours after placement of the transdermal fentanyl delivery system, this plateau was maintained until removal of the system at 48 hours **[22,31]**.

In the present study, this pharmacokinetic aspect of the TDF was taken into account, the TDF patches were placed about 10 hours before the surgery, so that the plateau was attained approximately at the end of the surgery. Thus, patients emerged from general anesthesia comfortable and without pain, explaining the low VAS score and morphine consumption in the immediate post-operative period. This is similar to the study previously done in which the TDF was placed 10 hours before surgery **[32]**.

There were several studies which did not take the pharmacokinetics of TDF into account. Like the studies of **Rowbotham *et al.* [33]** and **Sevarino *et al.* [25]**, which the TDF was placed only two hours before surgery**.** Also in the study by **Caplan *et al.* [34],** the TDF was placed just before surgery and in the study by **Gourlay *et al.* [35],** the TDF was placed during the surgery. In these studies the analgesic effect was commonly less apparent during the first 12 hours after application. The application and removal of the transdermal system was accompanied by slow changes in serum fentanyl levels**.**

Our study showed that there were significantly lower VAS scores and morphine consumption (including the frequency of morphine administration) throughout the period of the study in the TDF group.

Kilbride *et al.* [36] compared TDF (with delivery rate of 50ug/h) applied six hours before surgery and removed after 72 hours with placebo for the management of post-hemorrhoidectomy pain. They found that there were significant reduction in the pain intensity and rescue analgesia in the TDF group when compared with the placebo group.

Sevarino *et al.* [28] compared TDF in two different delivery rates 25 ug/h and 50 ug/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 of 25ug/h when compared with the placebo group. There was only a significant reduction in the rescue analgesia in the TDF group with a delivery rate of 50ug/h.

Also Sandler *et al.* [37] compared TDF in two different delivery rates 50 µg/h and 75µg/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 75µg/h when compared with the placebo group. But in the TDF group with delivery rate of 50µg/h there was only a significant reduction in rescue analgesic consumption when compared with the placebo group.

Transdermal fentanyl provided effective analgesia for acute postoperative pain. The VAS pain scores were consistently better in the fentanyl group compared with the placebo group, and these lower pain scores were strongly correlated with serum fentanyl concentrations. Although significant differences in pain scores between the groups were observed only at 12, 16, and 24 hours, a better indication of the efficacy of fentanyl was the significant 50–65% reduction in the requirement for bupivacaine among these patients compared with the placebo group **[6]**.

Transdermal fentanyl (50µg/h) was compared with patient-controlled analgesia (PCA morphine) for postoperative analgesia after total hip arthroplasty, the TDF group showed significantly diminished VAS score (3.7±2.2cm versus 7.3±1.3cm, P<0.0001) and morphine requirement (3.5±3mg versus 13±5mg, P<0.0001) as the patient arrived in the PACU when compared with PCA morphine group. The cumulative morphine consumption in 48 hour study period was significantly lower in the TDF group than in the PCA morphine group (5±4mg versus 54±26mg, P<0.0001) **[32]**. This is in consistent with the results in our study in which the TDF group showed a diminished VAS score in the immediate postoperative period (2.57±1.3cm) and the 1st time to administer morphine was 1.7±5.8 hour postoperatively with cumulative morphine consumption in 48 hour study period was only 2.5±3.65mg.

The efficacy of transdermal fentanyl delivery system for acute postoperative pain after posterior laminectomy was evaluated (by comparing between TDF 25µg/h, and placebo) and showed that the transdermal fentanyl group had 60% reduction in rescue analgesic consumption ($p < 0.05$); and displayed lesser VAS scores after the 12th hour, which maintained until the 36th hour postoperatively ($p < 0.02$). Also they reported that all physiological parameters fluctuated within normal range **[38]**.

Our results are also in agreement with a study performed by **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, 50µg/h, with placebo). VAS scores and rescue analgesic requirements were lower in transdermal fentanyl group ($p < 0.05$) **[39]**.

In our study all cases of the TDF group were hemodynamically stable. Sedation occurred only in the 1st 8 hours postoperatively and it was only in the form of drowsiness that was resolved spontaneously. There were no reported cases of erythema, respiratory depression or pruritus. Nausea and vomiting occurred only in 32 % of cases. Also there were no cases of respiratory depression.

In the TDF group with delivery rate of 75 µg/h the incidence of respiratory depression, sedation and nausea/vomiting were 11, 22 and 83% respectively **[25]**. Another study showed that, the incidence of respiratory depression was higher in the TDF group with delivery rate of 75µg/h (15%) than in the TDF group with delivery rate of 50µg/h **[37]**.

Minville *et al.* [32], reported that in the TDF group 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) [38]. Nausea occurred in (33.3%) of patients in the TDF group [39], which is different from our study where no any case of erythema was reported, and no respiratory depression was observed.

In the present study, there was an overall significant reduction in the VAS score in the TDF group when compared with the C group. Even in the 4th and 8th hours where there was no significant reduction of the VAS, it was still lower in the TDF group than the C group. This reduction in the VAS score was associated with significant reduction in the postoperative morphine requirement as compared with the other group.

There were no adverse events that necessitated patient withdrawal, and there was no evidence of respiratory depression with no patient had a marked low respiratory rate, CO_2 retention, or severe hypoxia in the two groups. Although some cases in both groups were having mild hypoxia and some degree of CO_2 elevation, they did not lost communication or consciousness and did not require any intervention, they improved by intermittent putting O_2 mask 40% for a few hours.

We conclude that transdermal administration of fentanyl 50 µg/h 10 hours preoperatively is an effective noninvasive and convenient technique for postoperative pain relief after major abdominal surgery and allows delivery of a potent analgesic agent with acceptable minimal side effects.

Corresponding author:
Dr. Samy A. Amr,
Associate Professor of Anesthesiology,
ICU, and Pain Management,
South Egypt Cancer Institute (SECI),
Assiut University, Egypt.
E-mail: saaerfan62@yahoo.com.ph

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