

Reducing Postoperative Opioid Consumption by Adding Transdermal Fentanyl Patches to Multimodal Analgesia after Breast Cancer Surgery

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Abstract

Background: Breast surgeries are among the common forms of surgeries that conducted daily in hospitals. Multimodal analgesia, which combines analgesics with variable pharmacodynamics to target multiple underlying mechanisms of pain, is evolving as an acceptable approach to pain treatment for acute pain. So Transdermal fentanyl patch (TDF) can ameliorate severe pain in breast surgery.

Objective: To examine the efficacy and safety of adding Transdermal fentanyl patch (TDF) to multimodal analgesia in controlling acute postoperative pain after breast surgery if applied 12 hours prior surgery.

Methods: This randomized, blinded, study was conducted after approval of local ethics committee of South Egypt Cancer Institute, Assiut University, Assiut–Egypt, and registered at www.clinicaltrials.gov at no.: "NCT03051503". After obtaining written informed consent, Sixty four adult female patients (ASA II) were scheduled for elective breast cancer surgeries in the form of modified radical mastectomy. Patients were classified randomly into two groups (32 patients each) to receive beside standard GA, Transdermal fentanyl patch (TDF) 50 µg/hr applied 12 hours prior surgery in one group (TDF group), while the second group (control group) received standard GA alone. Both group treated by morphine PCA for postoperative pain. Visual analogue scale (VAS), side effects, and serum levels of cortisol and prolactin were assessed over 24 h. postoperatively. The intra and post-operative heart rate (HR) and mean arterial pressure (MAP), Ramsay sedation score and total morphine consumption via PCA postoperatively were also recorded.

Results: MAP and heart rate during intra and early post-operative periods were significantly reduced in TDF group in comparison to control group ($P \leq 0.005$) but not over the remaining post-operative period ($P > 0.01$). And, there was significant decrease in both VAS scores ($p < 0.05$) and hence the total amount of morphine consumed postoperatively (7.43 ± 4.39) in TDF group in comparison to control group (13.47 ± 4.73) without significant change in side effects, except sedation scores, which were statistically increased but clinically not effective, in early post-operative hours. Finally, levels of prolactin and cortisol hormones were significantly decreased in TDF group indicating less stress and better pain control.

Conclusion: Applying Transdermal fentanyl patch (TDF) 50 µg/hr 12 hours prior surgery as a part of multimodal analgesia to control acute postoperative pain after modified radical mastectomy was associated with less stress response, better pain control and decreased total amount of postoperative morphine consumption.

Keywords: Breast cancer surgery; Transdermal fentanyl patch (TDF); Postoperative pain; VAS scale

Introduction

Breast cancer is by far the world's most common cancer among women and in Egypt, it represents 32% of all cancers among females [1,2]. Breast cancer surgeries are associated with moderate-to-severe pain on the first day after surgery (median score of 7 on the Numeric Rating Scale (NRS) [3]. Despite the increased awareness of pain management, postoperative pain is reported by about 80% of surgical patients [4]. Poorly controlled acute postoperative pain may result in a range of detrimental acute and chronic effects (i.e., adverse physiologic responses, delayed long-term recovery and chronic pain) [5]. With good analgesic treatment, pain intensity generally declines from moderate or severe to mild levels after the first 24–48 h after surgery [6]. Multimodal analgesia aims to get optimum effectiveness from the different agents in low dosages in order to minimize side effects from each analgesic. This important concept employs the theory that agents with different mechanisms of analgesia may have synergistic effects in treating acute pain [7]. During postoperative period, strong opioids analgesics may be used for relief of acute pain as it have high efficacy [8]. Intravenous (IV) rout of administration is the most common route used during the early postoperative period. In such cases, a multimodal drugs approach must be employed. This may include the administration of opioids, NSAIDS, and other adjuvant if needed in order to optimize acute pain control in

the immediate postoperative period as a bridge till the patient start oral medications [9,10].

Fentanyl is a synthetic opioid with low molecular weight that has high potency analgesic effect specially if through intravenous route and its analgesic potency is 50 to 100 times more than morphine. Due to its small molecule weight and high lipid solubility, fentanyl is a good choice for transdermal use [11]. The advantages of patch are; better flexibility, skin conformability, and produces linear fentanyl dose kinetics with negligible dose loading [12], and according to the pharmaceutical company is indicated for management of persistent moderate to severe pain [13]. Stress, whatever physical or emotional like pain, activates

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neurons that secrete corticotropin-releasing hormone, which results in higher plasma cortisol levels. Prolactin is also released in response to stressor stimuli, although its exact role in the response to stress is not known [14-16]. The aim of this study was to examine the efficacy and safety of adding Transdermal fentanyl patch (TDF) to multimodal analgesia in controlling acute postoperative pain after modified radical mastectomy if applied 12 hours prior surgery.

Patients and Methods

This randomized, blinded, study was conducted after approval of local ethics committee of South Egypt Cancer Institute, Assiut University, Assiut-Egypt, and registered at www.clinicaltrials.gov at no.: "NCT03051503". After obtaining written informed consent, Sixty four adult female patients (21-70 years old) ASA II with cancer breast, were scheduled for elective modified radical mastectomy.

Exclusion criteria were ASA III, VI, history of drug abuse, emergency, extremes of ages, pregnancy and mentally retarded patient, who cannot use PCA pump nor how to evaluate their own pain level.

Two days before surgery, preoperative data were collected including; demographic data, medical history, physical examination and results of routine laboratory investigations. One day before surgery, all enrolled patients were taught how to use Visual Analog Scale (VAS) to evaluate their own pain level. VAS scored from 0-10 (0=no pain and 10=worst pain ever) also how to use the patient controlled analgesia (PCA) device (Abbott Pain Management Provider. S. No: 96450292. Abbott Laboratory, North Chicago. IL: 60064, USA). All Patients were classified randomly into two groups (32 patients each). We used opaque sealed envelopes which contain computer generated schedule as a method of randomization, and the envelopes were sequentially numbered and opened before application of anesthetic plan. Premedication drugs given to all patients includes; midazolam 0.05 mg/kg and ranitidine 50 mg.

After shifting the patient to the operative theatre, basic monitoring was attached and peripheral venous line was established then an infusion of lactated ringer solution started.

Control group (No.=32)

Modified radical mastectomy was performed under standard general anaesthesia and postoperative analgesia was provided through intravenous patient controlled analgesia (PCA) for 48 hours postoperatively.

TDE group (No.=32)

Modified radical mastectomy was done under standard general anaesthesia and additionally Transdermal fentanyl patch 50 µg/h was applied 12 hours prior to the surgery by the duty anaesthesiologist who just placed the patch and fixed with plaster to prevent displacement and also labelled it with date and time of affixing. Postoperative analgesia was provided through PCA for 48 hours postoperatively.

Standard general anaesthesia

Pre-oxygenation for 3 minutes, then intravenous propofol 1.5-2 mg/kg induced with fentanyl 2 µg/kg administered over min. Tracheal intubation was facilitated by neuromuscular blocking agent (cisatracurium 0.15 mg/kg). All patients received ketorolac (30 mg) and Paracetamol (1 gm), I.V. after induction as pre-emptive analgesia.

Anesthesia maintenance was done by sevoflurane 1-1.5 MAC, cisatracurium 0.03 mg/kg given when indicated. All patients were mechanically ventilated aiming to maintain ETCO₂ between 35-40

mmHg. The inspired oxygen fraction (FIO₂) was 0.5 using oxygen-and-air mixtures. At the end of surgery neuromuscular block was reversed in all patients using neostigmine 0.05 mg/kg and atropine 0.02 mg/kg and extubation was done in the operating room when patients met the following criteria: hemodynamic stability, adequate muscle strength, full consciousness, adequate ventilation breathing rate: 10 to 30 breaths/min and PaCO₂, 30 to 45 mmHg).

All patients received post-operative ketorolac 30 mg/12 hours, Paracetamol 1 gm/8 hours and, Morphine was given for rescue analgesia *via* PCA which was adjusted as following; 1 m / dose with lockout interval of 10 min with no background infusion. The analgesic regimen was adjusted to achieve a visual analog scale scores less than 3. Intra-operatively, patients of both groups were followed up for vital signs (heart rate, mean blood pressure) and the mean reading every one hour was recorded.

Post-operative: All patients were admitted to surgical department and beside routine follow up, the following were recorded:

- HR and MAP were recorded for 24 hours
- Visual analogue scale (0-10) where 0=no pain 10=worst pain ever -every 4 hours for 2 days- for pain measurement, and total post-operative morphine consumption was calculated.
- Ramsay Sedation Score was assessed one day postoperatively by 5 points as following 0=aware -1=drowsy -2=asleep/easily respond to verbal command -3=asleep/difficulty responding to verbal command -4 = asleep/no respond to verbal command.
- Nausea and vomiting scores 0=none, 1=mild, 2=moderate and 3=severe.
- Pruritus; Present=1 or Absent=0.
- Respiratory depression (decrease oxygen saturation \geq 90% or respiratory rate less than 8) were recorded post-operatively.
- Cortisol and prolactin serum levels at immediately post-operative, 1 hour and 24 hours post-operative.

Statistical Analysis

The sample size was calculated using Epi Info software version 8 (CDC, 2014). With total morphine consumption as the primary outcome to achieve a power of 80% to detect an effect size of 0.8 in the outcome measures of interest, assuming a type I error of 0.05 and therefore, it was estimated that minimum sample size of 32 patients in each study group.

All analyses after cleaning by EXCEL[®] program were performed using the SPSS 21[®] software. Categorical data were described as number and percent (N, %), where continuous data described as mean and standard deviation (Mean, SD). Mann-Whitney test were used to compare between two groups while Chi square test was used for qualitative data. Where compare between continuous data by t-test. P was considered significant if ≤ 0.05 at confidence interval 95%.

Results

In this study; seventy adult female patients enrolled to do modified radical mastectomy and randomly classified into 2 groups (35 patients in each group), sixty four patients of them were finally analysed, the TDF Group (n=32) and control Group (n=32).

Figure 1 illustrates the flow of the patients through the study. The demographic data of the patients were similar between groups (Table 1).

Regarding intra operative MAP and heart rate, there was statistical significant reduction in patients of TDF group in comparison to control group patients at intra operative specially 1st and 2nd hours ($P \leq 0.05$), but the baseline readings there were no significant differences ($P > 0.05$) as shown in the Figures 2 and 3.

Post-operative heart rate and MAP were reduced significantly in patients of TDF group compared to control group patients in the early postoperative period ($P > 0.01$) as shown in Table 2.

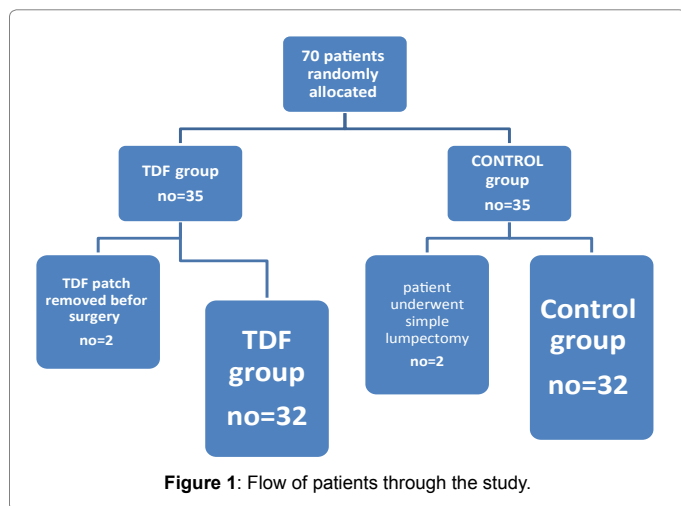
And, there were significant decreased in both VAS scores ($p < 0.05$) and the total amount of postoperative morphine consumption (7.43 ± 4.39) in TDF group in comparison to control group (13.47 ± 4.73) as shown in Tables 3 and 4 without significant change in side effects (Figure 4), except sedation scores, which was statistically increased but clinically not effective, in early post-operative hours (Table 5).

Finally, levels of prolactin and cortisol hormones were significantly decreased in TDF group indicating less stress and better pain control as shown in Tables 6 and 7.

Discussion

Surgery remains the first choice in the treatment of solid neoplastic tumours including breast tumours [17]. And according to McCaffery et al. who showed that, over 50% of surgical patients experienced inadequate pain relief following surgery with negative physiological and psychological consequences [18]. Fentanyl has the following advantages; high lipophilicity, has a short duration of action with lower incidence of side effects, and less risk of respiratory depression make it good choice for acute pain management [7]. The transdermal fentanyl patch (TDF) is a skin-patch opioid that releases dose-dependent fentanyl into the bloodstream in a steady manner [19]. It provides a stable plasma level similar to intravenous (IV) use. TDF has a slow onset and this is why it is commonly used for chronic pain management [20]. This clinical trial showed that patients of TDF group had better analgesia during first hours after surgeries in comparison to control group with good control of both intra and post-operative HR and MAP and tolerated side effects except sedation scores which were significantly high. The total doses of post-operative morphine consumption were significantly lower in the TDF than in the control group.

Recently, patient-controlled analgesia (PCA) systems have been established as a standard treatment for moderate to severe post-operative pain [21], instead of traditionally intramuscular (IM) or intravenous (IV) boluses of opioid analgesics and up to 30% of



	Control group (NO.=32)	TDF group (NO.=32)	P. value
Age (years)			
Range	31-69	28-70	0.184
Mean ± SD	54.3 ± 6.1	57 ± 9.14	
Weight (kg)			
Range	60-86	54-84	0.259
Mean ± SD	70.5 ± 7.35	68.13 ± 8.68	
Height (cm)			
Range	150-180	152-178	0.055
Mean ± SD	167.13 ± 6.7	163.77 ± 6.61	
BMI (kg/m²)			
Range	18.73-33.3	17.92-34.96	0.794
Mean ± SD	25.37 ± 3.46	25.5 ± 3.7	
Site of surgery			
Right	17	14	0.844
Left	15	18	
Duration of anesthesia (minutes)			
Range	121-169	115-177	0.738
Mean ± SD	148.13 ± 6.7	139.77 ± 7.61	

Data are expressed as mean ± SD, TDF=Trans dermal fentanyl group. BMI=body mass index. P. value<0.05 considered statistically significant.

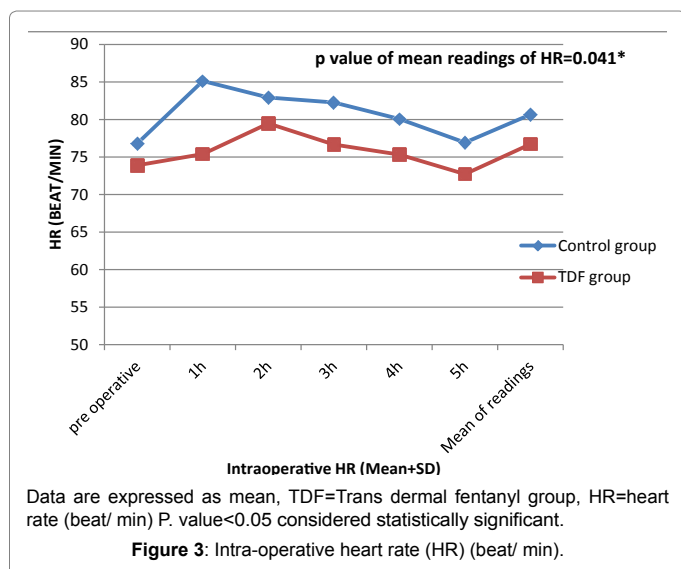
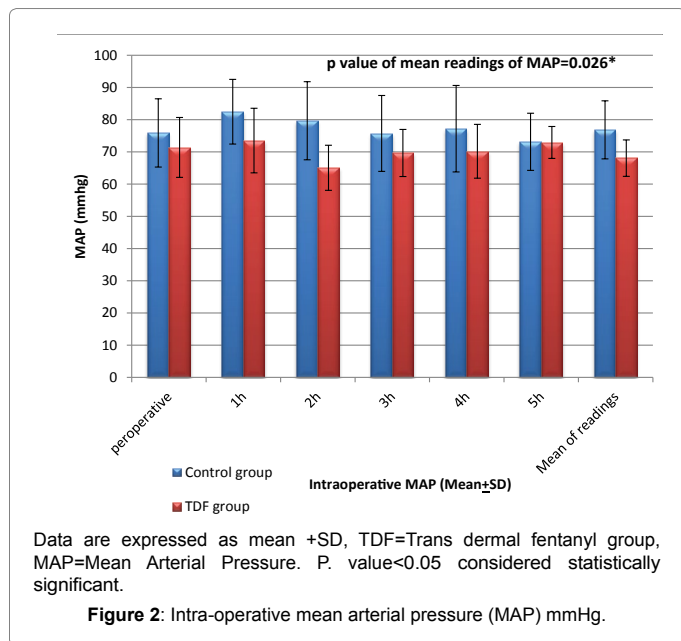
Table 1: Demographic data of both groups.

	Control Group		TDF Group		P. value
	Range	Mean ± SD	Range	Mean ± SD	
HR (bpm)					
0.5 h	60-106	72.13 ± 9.61	65-108	80.33 ± 9.97	0.002**
1 h	60-110	70.6 ± 10.13	65-110	78 ± 10.65	0.019*
2 h	60-95	75.27 ± 8.2	63-106	79.8 ± 11.77	0.089
4 h	60-99	78.37 ± 10.42	65-103	82.53 ± 8.91	0.101
8 h	69-103	81.53 ± 8.01	60-100	82.8 ± 9.76	0.586
12 h	66-108	82.3 ± 9.1	70-97	83 ± 7.76	0.751
24 h	71-98	83.07 ± 6.73	69-100	82.67 ± 7.49	0.449
MAP (mmhg)					
0.5 h	70-100	87.33 ± 7.96	70-95	80 ± 7.8	0.001**
1 h	70-110	85.5 ± 11.17	70-90	71.83 ± 7.48	0.006**
2 h	70-110	87.5 ± 9.63	70-100	84.83 ± 7.13	0.228
4 h	80-110	89.17 ± 9.01	70-100	86.67 ± 9.86	0.326
8 h	70-105	90.5 ± 8.74	70-110	91 ± 7.81	0.816
12 h	70-110	88.33 ± 8.24	70-115	90.67 ± 10.06	0.330
24 h	75-100	86.5 ± 6.97	70-105	91.83 ± 7.6	0.140

Data expressed as (Mean ± SD) and range TDF=Trans dermal fentanyl group, MAP=Mean Arterial Pressure. HR=heart rate, bpm=beats/ min. P. value<0.05 considered statistically significant.

Table 2: Postoperative heart rate (beats/ min) and MAP (mmhg).

patients given IM or IV analgesia report severe post-operative pain, reducing to around 10% in patients treated post operatively with PCA systems. Also it may lead to analgesic overdose and toxicity beside these methods are invasive, requiring a needle for administration, introducing the risks of needle-stick injury and infection to the patient and hospital personnel [22]. Our study investigated the effectiveness of incorporating the application of low dose transdermal fentanyl patch



Post-operative VAS	Control group		TDF group		P. value
	Range	Mean ± SD	Range	Mean ± SD	
VAS at 0 h	1 - 3	2.1 ± 1	1 - 2	1.8 ± 0.9	0.009*
VAS at 4 h	1 - 4	2.4 ± 0.9	1 - 2	1.9 ± 0.5	0.005*
VAS at 8 h	1 - 4	2 ± 0.5	1 - 3	2.4 ± 0.5	0.019
VAS at 12 h	2 - 3	3 ± 0.8	1 - 3	2.4 ± 0.8	0.016
VAS at 16 h	1 - 3	2.5 ± 0.8	1 - 3	2.4 ± 1.1	0.577
VAS at 20 h	1 - 4	2.5 ± 0.9	1 - 3	2.3 ± 0.7	0.527
VAS at 24 h	2 - 4	3.2 ± 1	2 - 3	2.7 ± 0.9	0.158
VAS at 32 h	2 - 4	3.1 ± 0.8	1 - 3	2.7 ± 1.1	0.177
VAS at 40 h	1 - 4	2.5 ± 0.9	1 - 3	2.3 ± 0.7	0.527
VAS at 48 h	1 - 3	2.4 ± 0.6	1 - 3	2.6 ± 0.9	0.319

Data expressed as (Mean ± SD) and range TDF=Trans dermal fentanyl group, P. value<0.05 considered statistically significant.

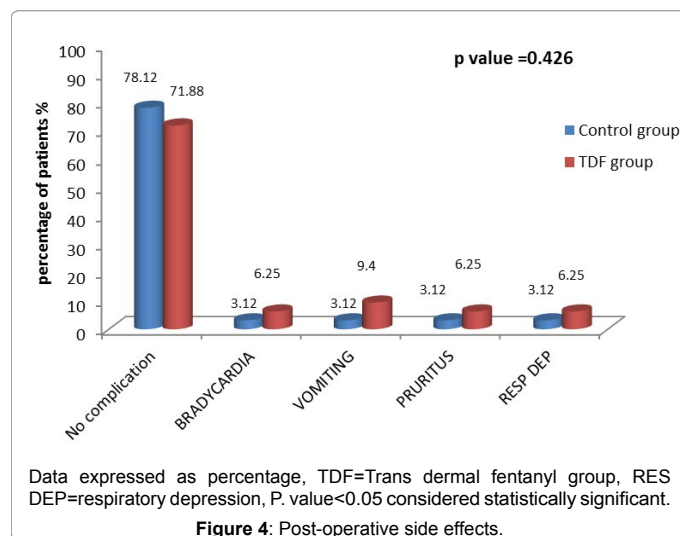
Table 3: Post-operative VAS scores.

into the multimodal analgesia model and its effectiveness in achieving maximum patient comfort with minimum complications. Sebel et al.

	Control Group		TDF Group		P. value
	Range	Mean ± SD	Range	Mean ± SD	
Total P.O. morphine consumption (mg)	0-16	9.47 ± 2.73	0-9	4.43 ± 2.39	0.001**

Data expressed as (Mean ± SD) and range TDF=Trans dermal fentanyl group, P. value<0.05 considered statistically significant.

Table 4: Total post-operative morphine consumption.



Post-operative sedation score	Control group		TDF group		P. value
	Range	Mean	Range	Mean	
0 h	(1-2)	2	(1-3)	2	0.09*
4 h	(1-1)	1	(1-2)	2	0.00*
8 h	(1-1)	1	(1-2)	2	0.956
12 h	(1-1)	1	(1-2)	1	0.743
16 h	(1-1)	1	(1-2)	1	0.548
20 h	(1-1)	1	(1-2)	1	0.910
24 h	(1-1)	1	(1-2)	1	0.956

Data expressed as (Mean and range). TDF=Trans dermal fentanyl group, P. value<0.05 considered statistically significant.

Table 5: Post-operative sedation score.

Prolactin level	Control group	TDF group	P. value
Immediately			
Range	3-140	3-140	0.386
Mean ± SD	38 ± 42.8	42.4 ± 41.4	
After 1 h			
Range	4-156	4-125	<0.001**
Mean ± SD	79.9 ± 50.1	31.6 ± 25.7	
After 24 h			
Range	4-140	3-105	0.009**
Mean ± SD	65.8 ± 42.1	28.3 ± 22.1	

Data expressed as (Mean ± SD) and range TDF=Trans dermal fentanyl group, P. value<0.05 considered statistically significant.

Table 6: Prolactin levels in the studied groups (ng/ml).

described transdermal fentanyl patch for first time in 1987 [23], and in fact fentanyl was the first opioid commercially available for transdermal administration. The Food and Drug Administration (FDA) has granted limited approval of its use for patients complaining of chronic cancer pain [24]. Regarding transdermal fentanyl use in the management of

Cortisol level	Control group	TDF group	P. value
Immediately			
Range	80-700	60-800	0.765
Mean ± SD	289.2 ± 206.3	277 ± 203.4	
After 1 h			
Range	140-1100	90-800	0.001**
Mean ± SD	433.7 ± 236.6	298.5 ± 65.0	
After 24 h			
Range	100-950	80-710	0.047*
Mean ± SD	305.2 ± 187.5	257.3 ± 163.2	

Data expressed as (Mean ± SD) and range. TDF=Trans dermal fentanyl group, P. value<0.05 considered statistically significant.

Table 7: Cortisol levels in the studied groups (micg/dl).

acute pain like this study, Gourlay et al. [25], approved that the efficacy of transdermal fentanyl in the treatment of acute pain following abdominal surgery. Also, Lehmann et al. [26], who concluded that patients who received transdermal fentanyl required significantly less additional fentanyl and reported less pain than patients in the placebo group following major urological operations.

According to Van Bastelaere et al. [27], transdermal fentanyl patches were convenient and its use is easy because each patch can be left in place for 3 days with stable plasma fentanyl concentrations. For these reasons, he selected the transdermal fentanyl patch for his study of post-operative pain management following total knee arthroplasty (TKA). In agreement with us, Minville et al. [28] who found that a 50 µg/hr TDF, placed 10 h preoperatively, was very effective in decreasing both the pain severity and the consumption of rescue morphine in patients undergoing total hip arthroplasty for 24 hours post-operative. Also, Abrisham et al. [29], reported that two 25 µg/hr TDFs (which equal 50 µg/hr TDF), which were placed simultaneously on the lateral chest wall approximately 12 hours preoperatively, resulted in effective pain relief and decreased the total post-operative morphine consumption during the first 72 hours after total knee arthroplasty (TKA) surgery without adverse side effects. In post-operative cancer patients, Osipova et al. studied the effect of preoperative TDF in thoracoabdominal oncological surgery for prevention and treatment of acute post-operative pain syndromes, and concluded that TDF prevent early post-operative acute opioid tolerance and hyperalgesia. Increasing the benefit of TDF use in multimodal analgesia with NSAID and this confirm our findings [30]. Regarding side effects of TDF, many studies have concluded that; we should pay attention to the side effects associated with the use of the transdermal fentanyl patch specially in opioid naive patients. [31]. Sandler et al. [32], who reported that a TDF 75 µg/hr when used in patients undergoing abdominal hysterectomy, was associated with a high incidence of respiratory depression, requiring intensive monitoring and oxygen supplementation. Also Van Bastelaere et al. [27], who noticed the efficacy of transdermal fentanyl for post-operative pain relief following orthopaedic surgery, but reported that intense respiratory depression was sometimes seen in some patients.

According to Apfel et al. [33], the incidence of post-operative nausea and vomiting (PONV) is high when he used TDF 75 µg/hr in his study. This is mainly explained by administration of emetogenic stimuli, such as volatile anaesthetics and high dose fentanyl (75 µg/hr). So we used in our study TDF patch in concentration of 50 µg/hr instead of 75 µg/hr to decrease PONV. We preferred to put TDF patch 12 hours before surgery to get steady plasma level in Sevarino et al found significantly better analgesia with 50 µg/hr fentanyl patches as compared to the 25 µg/hr patch, but the patch was place only one hour before the start of surgery and was the sole analgesic used. This was why we used the 50

µg/hr fentanyl patch and found it to provide adequate pain relief [34]. A prospective multi-center randomized controlled trial comparing the fentanyl transdermal to IV PCA morphine in 650 patients demonstrated identical patient global assessment of pain control, with over 80% of patients reporting good or excellent pain relief in both treatment arms following major abdominal or orthopedic surgery, with similar pain intensity scores and side-effects reported in both groups [35]. Similar satisfaction and pain intensity score reporting was repeated in further active-comparator [36,37].

Several lines of evidence suggest that stress is characterized by increased levels of cortisol and inhibits NK cell activity. In fact, these are the cells most susceptible to the effects of cortisol, and their activity is considered to be a reliable indicator of the cell immunity suppression caused by stress. Based on these lines of evidence, we were interested in determining whether the presence of post mastectomy pain is associated with increased these stress hormones as an objective tool of assessment. So decrease in the levels of these hormones as in our study confirm the fact of better pain control in TDF group [38,39].

Conclusion

Applying Transdermal fentanyl patch (TDF) 50 µg/hr, 12 hours prior surgery as a part of multimodal analgesia to control acute postoperative pain after modified radical mastectomy was associated with less stress response, better pain control and decreased total amount of postoperative morphine consumption.

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