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 ≤ 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) route 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...
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=awake -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 ≥ 90% or respiratory rate less than 8) were recorded post-operatively.
• Cortisol and lactotropin 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 (CD C, 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 60.05 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 intraoperative 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 ≤ 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 chronic pain management [19]. This clinical trial showed that patients of TDF group had better analgesia during first hour 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 [20], instead of traditionally intramuscular (IM) or intravenous (IV) boluses of opioid analgesics and up to 30% of 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 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 chronic pain management [19]. This clinical trial showed that patients of TDF group had better analgesia during first hour 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.

|        | 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 |
|--------|---------------|-----------|----------|
| HR (bpm) | Range | Mean ± SD | Range | Mean ± SD |
| 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) | Range | Mean ± SD | Range | Mean ± SD |
| 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 | 70-110 | 86.67 ± 9.86 | 0.326 |
| 8 h | 70-105 | 90.5 ± 6.74 | 70-110 | 91 ± 7.81 | 0.816 |
| 12 h | 70-110 | 85.33 ± 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).

Figure 1: Flow of patients through the study.

Vital signs were monitored every 2 h (70-105) for MAP and HR in control group and every 2h (70-110) for MAP and HR in TDF group. No complications were observed in the study period. Postoperative pain was assayed at 1 h intervals for the first 24 h viaVisual Analog Scale (VAS) visual scale, which ranges from 0 to 100 mm, where 0 mm means no pain and 100 mm means worst possible pain. Furthermore, level of sedation was assessed before and after administration of medications using the sedation scores. The scores were recorded before sedation (first score) and after sedation (second score). If the difference of the two scores is lower than 4, then the patient is awake and alert (score 1); if the difference is between 4 and 7, then the patient is sleepy and requires light sedation (score 2); if the difference is greater than 7, then the patient is deeply sedated (score 3). The patients were visited postoperatively at 12, 24, 48, and 72 h for follow-up visits. During each visit, vital signs and pain scores were assessed. In addition, levels of prolactin and cortisol hormones were estimated at 48 and 72 h postoperatively. The prolactin level was estimated using the electrochemiluminescence immunoassay (ECLI) method, while the cortisol level was estimated using the hemagglutination inhibition (HAI) method.

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 ≤ 0.05), but the baseline readings there were no significant differences (P>0.05) as shown in the Figures 2 and 3.
2.4 + maximum patient comfort with minimum complications. Sebel et al. into the multimodal analgesia model and its effectiveness in achieving maximum patient comfort with minimum complications. Sebel et al. 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...
akute 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, Abirsham 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 total knee arthroplasty (TKA) surgery without adverse side effects. For patients reporting good or excellent pain relief in both treatment arms of a double-blind, randomized, placebo-controlled trial, Minville et al. [30] found that 50 μg/hr TDF, placed 10 h preoperatively, was very effective in decreasing 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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| 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     | 140-1100      | 90-800    | 0.001**  |
| Mean ± SD     | 433.7 ± 236.6 | 298.5 ± 65.0 |          |
| After 24 h    | 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 (mcg/dl).
