Research Article

Comparative study between transdermal fentanyl and melatonin patches on postoperative pain relief after lumber laminectomy, a double-blind, placebo-controlled trial

CrossMark

Ibrahim M. Esmat [a],*, Dina Y. Kassim [b]

[a] *Lecturer of Anesthesia and Intensive Care Medicine, Ain Shams University Hospitals, 29-Ahmed Fuad St., Saint Fatima Square, Heliopolis, Cairo 11361, Egypt*
[b] *Lecturer of Anesthesia and Intensive Care Medicine, Beni Sweif University Hospitals, El Rehab City, Group 71, Building 15, New Cairo 11841, Egypt*

Abstract *Background:* This study evaluated the efficacy of transdermal fentanyl (TDF) delivery system (50 μg/h) or transdermal melatonin (TDM) delivery system (7 mg) 2 h preoperatively for acute postoperative pain after lumbar laminectomy compared to placebo group (C).
Methods: Seventy-five patients of both sexes, aged 18–50 years, ASA I and II undergoing elective single level lumber laminectomy under general anesthesia were included in this randomized controlled double-blind study. Patients were randomly divided into 3 groups 25 each, C group patients received transdermal placebo patch, TDF group (50 μg/h) and TDM group (7 mg). Assessment of postoperative pain, sedation, hemodynamic variables such as HR and MAP, postoperative monitoring of arterial SpO_2 and side effects (e.g. nausea, vomiting, pruritis, respiratory depression and hemodynamic instability) was done 30 min, 1, 2, 6 and 12 h postoperatively. Postoperative Patient‛s and Surgeons‛ satisfaction, Intraoperative bleeding and plasma cortisol (μg/dl) postoperatively were also assessed.
Results: There was a significant reduction in the VAS score, total pethidine requirements and significantly higher Patient‛s satisfaction in TDF and TDM groups when compared with the C group 6 h postoperatively. The sedation score and Surgeons‛ satisfaction were significantly higher associated with a significant decrease in MAP and Intraoperative bleeding in TDM group compared to groups C and TDF 6 h postoperatively. Significant nausea and vomiting in TDF group and significant sedation in TDM group were recorded.

* Corresponding author at: Lecturer of Anesthesia and Intensive Care Medicine, Ain Shams University Hospitals, 29-Ahmed Fuad St., Saint Fatima Square, Heliopolis, Cairo 11361, Egypt. Tel.: +20 0227748551, +20 01001241928.
E-mail addresses: himadouh@hotmail.com (I.M. Esmat), dinayk31@yahoo.com (D.Y. Kassim).

Conclusion: The use of preoperative TDF 50 µg/h or TDM 7 mg was an effective and a safe adjuvant for acute pain after surgery.

1. Introduction

"Freedom from pain should be a basic human right, limited only by our knowledge to achieve it" [1]. Central sensitization and hyperexcitability develop after the surgical incision resulting in amplification of postoperative pain [2]. Kissin introduced the term 'preventive analgesia' to emphasize the fact that central sensitization is induced by noxious preoperative and postoperative inputs [3,4]. McCaffery and Ferrell showed that over 50% of surgical patients experienced inadequate pain relief following surgery with negative physiological and psychological consequences [5]. Surgical injury elicits a well-known stress response involving activation of inflammatory, endocrine, metabolic and immunologic mediators [6]. 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 [2]. These concepts suggest a possible study design; effective analgesia starts before incision and covers both the period of surgery and the postoperative period.

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 [7].

Fentanyl citrate is a potent synthetic narcotic with physicochemical characteristics that are suitable for rate controlled transdermal delivery. These characteristics include high potency, skin compatibility, low molecular weight, and appropriate solubility [8]. Transdermal delivery system for fentanyl (TDF) has been developed and approved for the treatment of cancer and chronic pain and it has been demonstrated that transdermal fentanyl provides effective analgesia for acute postoperative pain. TDF does not require I.V. access and the risk of infection is decreased [9]. Fentanyl patches are designed to deliver fentanyl at four constant rates: 25, 50, 75, and 100 µg/h for a period of 72 h. The steady-state serum concentration is reached after 24 h and maintained as long as the patch is renewed [10]. The choice of the transdermal delivery system of fentanyl with a predicted delivery rate of 50 µg/h 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 25 µg/h [11–14]. On the other hand, up to 9% of patients were at risk of respiratory depression when being treated with TDF 75 µg/h (administered 8 h prior to surgery) [14]. For management of postoperative pain, it may be desirable to apply transdermal fentanyl several hours before completion of surgery so that minimal effective concentration (MEC) can be achieved prior to or concomitant with the end of surgery [15].

Melatonin (*N*-acetyl-5-methoxytryptamine, MT) is a hormone secreted primarily by the pineal gland in a circadian fashion. The synthesis and secretion of MT is induced by darkness and suppressed by light through retinal nerve fibers projecting to the suprachiasmatic nucleus of hypothalamus, then to the superior cervical ganglion and finally to the pineal gland. During the night, the mean endogenous plasma concentration of MT is ~50–70 pg/mL (216–302 pmol/L) in young adults. In daylight hours, the mean MT plasma concentration is typically < 10 pg/mL (43 pmol/L). Plasma MT levels typically begin to increase at ~2100 h, peak between 0200 and 0400 h, and return to baseline at 0700–0900 h [16]. MT has a short plasma elimination half-life, ~45 min, and, when administered orally, shows low and variable bioavailability, presumably due to extensive first-pass metabolism and/or variable absorption [17]. Transdermal delivery system for melatonin (TDM) results in sustained plasma MT levels that can be tailored to the normal physiological range and avoid the first-pass metabolism. TDM is intended to be worn for 8 h [18]. Melatonin has sedative, anxiolytic, analgesic, antihypertensive, anti-inflammatory, chronobiotic and oncostatic effects and potent antioxidant properties [19]. Melatonin exerts its analgesic effects through augmentation of GABA-ergic systems and morphine anti-nociception, enhancing GABA-induced currents and inhibiting glycine effects [20]. Melatonin may enhance the levels of β-endorphins and the anti-nociception induced by delta opioid receptor agonists and could activate MT2 melatonin receptors in the dorsal horn of the spinal cord [21,22].

Spine surgery may range from minimal invasive discectomy surgery to extended scoliosis fusion. Both an anterior approach and posterior approach are possible. The most commonly used technique to anesthetize patients scheduled for thoracic or lumbar spine surgery is general anesthesia followed by conventional pain therapy [23]. Controlling the hemodynamic situation of patients who have spinal operation is of prime importance and maintaining the heart rate and blood pressure in normal or low-normal levels in these patients can reduce bleeding in the surgical field, particularly in congested, small and limited areas such as spine [24].

Surgical trauma elicits endocrine and metabolic changes characterized by an increase in the secretion of catecholamines. Pain and other afferent neurogenic stimuli from the site of the operation are known to play a dominant role in this mechanism [25,26]. The stress response to surgery is characterized by increased secretion of pituitary hormones and activation of the sympathetic nervous system. The changes in the pituitary secretions have secondary effects on hormone secretion from target organs (increased secretion of cortisol from the adrenal cortex) [27].

In this randomized, double-blind, placebo-controlled study, our primary goal was to compare the transdermal fentanyl patches to transdermal melatonin patches for relieving postoperative pain after single level lumber laminectomy under

general anesthesia to detect a mean difference of total analgesic (pethidine) consumption. And our secondary goal was to compare the effects of the transdermal fentanyl patches to transdermal melatonin patches on prolongation of first analgesic requirement time, pain score, sedation score, stress response, patient satisfactory score, surgeon satisfactory score, postoperative monitoring of heart rate, mean arterial blood pressure, arterial SpO_2 and side effects (e.g. nausea, vomiting, pruritis, respiratory depression and hemodynamic instability).

2. Methods

This study was designed to be a randomized, placebo-controlled, double-blind parallel study in which the patients, investigators, anesthesiologists and the surgeons were blinded to the given treatment. This study was conducted in Ain-Shams University Hospitals, from March 2013 to April 2015 on 75 patients aged between 18 and 50 years of both sexes of ASA physical status I and II of 70–90 kg body weight and height 160–180 cm undergoing elective single level lumber laminectomy under general anesthesia. The study protocol was approved by the institutional ethical committee and written informed consent was obtained from all the patients.

Patients with impaired kidney or liver functions, history of cardiac or central nervous system disease, history of drug or alcohol abuse, history of chronic pain or daily intake of analgesics, uncontrolled medical disease (diabetes mellitus and hypertension), history of intake of non-steroidal anti-inflammatory drugs or opioids within 24 h before surgery or allergy to the used medications, coagulation defect, local infection at the site of application of transdermal patch, patient refusal or duration of surgery more than 120 min were excluded from the study.

Patients were randomly divided into 3 groups, C group, ($n = 25$) each patient received transdermal placebo patch, TDF group, ($n = 25$) each patient received transdermal therapeutic system-fentanyl 50 μg/h and TDM group, ($n = 25$) each patient received transdermal therapeutic system containing 7 mg of melatonin. Randomization was done using computer-generated number table of random numbers in a 1:1 ratio and conducted using sequentially numbered, opaque and sealed envelope (SNOSE). All patches were placed 2 h preoperatively and were applied to the skin in the subclavicular area and 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 12 h postoperatively. In this study we used identical placebo patches assembled by the hospital pharmacy, and we used fentanyl patches [Durogesic® D-Trans® (matrix) from Janssen-Cilag] with delivery rate of 50 μg/h patch and we used melatonin sleep patch from Respro Labs™ containing 7 mg of melatonin. Active patches containing fentanyl or melatonin were indistinguishable from placebo patches, covered with adhesive plaster to confirm fixation and to blind the anesthetists and observers for the type of the used patches. The study drugs were prepared by the anesthesia resident not involved in any other part of the study.

Before any patch placement a preoperative visit was done to all patients to assess patient fitness for operation, to alleviate anxiety, to inform them about transdermal patches (its efficacy in the treatment of postoperative pain, its possible side effects and method of application) and to make them familiarized with 10 cm marked visual analog scale (VAS) for postoperative assessment of pain, where 0 cm defines no pain and 10 cm defines the maximum intolerable pain. The patients were also assured that they would receive intramuscular injection (IM) of pethidine 0.5 mg/kg once they start to first experience pain postoperatively (Patients with VAS > 3). Time to the first request for analgesic and the total pethidine consumption were recorded 12 h postoperatively.

The general anesthesia technique was standardized for all the patients as well as monitored including 5 lead ECG, non-invasive blood pressure (NIBP) monitor, pulse oximetry and capnography after intubation using Datascope monitors. Neuromuscular function was also monitored using a peripheral nerve stimulator. After establishing an intravenous (IV) line, induction of general anesthesia with fentanyl (2 μg/kg) and sleeping dose of propofol followed by rocuronium (0.6 mg/kg) to facilitate orotracheal intubation was done. Anesthesia was maintained using sevoflurane in oxygen and air. Granisetron (1 mg IV) was given as a prophylactic antiemetic. At the end of the surgery, the residual neuromuscular paralysis was antagonized with neostigmine (0.05 mg/kg) and atropine (0.01 mg/kg). After satisfactory recovery, patients were extubated and transferred to the post-anesthesia care unit (PACU) where they were monitored with ECG, NIBP and pulse oximetry.

Assessment of postoperative pain, sedation, hemodynamic variables such as heart rate (HR) and mean arterial pressure (MAP), postoperative monitoring of arterial SpO_2 and side effects (e.g. nausea, vomiting, pruritis, respiratory depression and hemodynamic instability) were done 30 min, 1, 2, 6 and 12 h postoperatively.

Postoperative pain was evaluated based on visual analog scale, first time to ask for rescue analgesia and total pethidine requirements in 12 h (mg) postoperatively were also recorded. Assessment of sedation was according to sedation score (Ramsay sedation score) [28] (see Table 1).

Hypotension was considered if there was 20% decrease below the baseline for mean arterial blood pressure, and it was treated with intravenous ephedrine (3–6 mg IV bolus). Bradycardia (heart rate < 55 beats/min) was treated with intravenous atropine (0.6–1 mg). If there was a decrease in arterial SpO_2 (< 90%), it was treated with oxygen through a transparent face mask. Severe nausea or vomiting was treated with dexamethasone 5 mg and severe pruritus was treated with clemastine (Tavegyl®) 2 mg/ampoule i.v. as required. If any of the patients developed respiratory depression, the transdermal patch was removed and intermittent doses of naloxone 40 mg i.v. were administered.

Table 1 Ramsay sedation score.

Score	Observation
1	Anxious, agitated or restless
2	Cooperative, oriented and tranquil
3	Responsive to commands
4	Asleep, but with brisk response to light glabellar tap or loud auditory stimulus
5	Asleep, sluggish response to glabellar tap or auditory stimulus
6	Asleep, no response

Likert scale:

1	2	3	4	5	6	7
Extremely dissatisfied	Dissatisfied	Somewhat dissatisfied	Undecided	Somewhat satisfied	Satisfied	Extremely satisfied

Figure 1 A 7-point Likert-like verbal rating scale for assessment of patients' and surgeons' satisfaction.

Table 2 Intraoperative bleeding score classification.

Score	Descriptions
0	No bleeding
I	Slight bleeding, no suctioning of blood required
II	Slight bleeding, occasional required suctioning. Surgical field not threatened
III	Slight bleeding, frequent suctioning required. Bleeding threatens surgical field a few seconds after suction is removed
IV	Moderate bleeding, frequent suctioning required. Bleeding threatens surgical field directly after suction is removed
V	Severe bleeding, constant suctioning required. Bleeding rate is faster than its removal by suctioning as surgical field is severely threatened and surgery becomes impossible

Patient's satisfaction was done by asking the patient to answer the question, 'How would you rate your experience after the surgery?' using a 7-point Likert verbal rating scale (Fig. 1) [29]. Surgeons were also asked to rate their satisfaction with operative conditions, using the 7-point Likert verbal rating scale at the end of surgery, acceptable satisfaction score of both the patient and surgeon being 5–7. Intraoperative bleeding was assessed by bleeding scale (0–5) (Table 2) [30], acceptable bleeding score being 0–2.

Hormonal stress response was assessed through recording plasma cortisol (micrograms/dl) 2 h postoperatively. Serum cortisol was measured by a Fluorescence Polarization Immunoassay (FPIA) Technology by the Abbott AXSYM system with the following reference ranges (morning serum cortisol 4.2–38.4 μg/dl and evening serum cortisol 1.7–16.6 μg/dl).

2.1. Analysis of data

Using PASS 13 for sample size calculation, in a one-way ANOVA study it was calculated that a sample size of 22 patients per group will achieve 80% power to detect a mean difference of 50 mg in total Pethidine consumption with a SD of 25 between the three groups using an *F* test with a 0.05 significance level. 25 patients per group were intended to be included to replace any dropouts.

Data were analyzed using SPSS 18.0 for Windows (SPSS, Chicago, IL, USA). Analysis of variance was used to compare quantitative parametric data with Tukey's test as a post hoc test. Kruskal–Wallis test was used for quantitative nonparametric data. Chi square test was used for comparison of qualitative data. Continuous parametric data were presented as mean ± SD, non-parametric data as median (IQR) and categorical data as number of patients. *P*-values of < 0.05 were considered statistically significant.

3. Results

A total of 85 patients were assessed for eligibility from March 2013 to April 2015 (Fig. 2), out of which 78 patients received
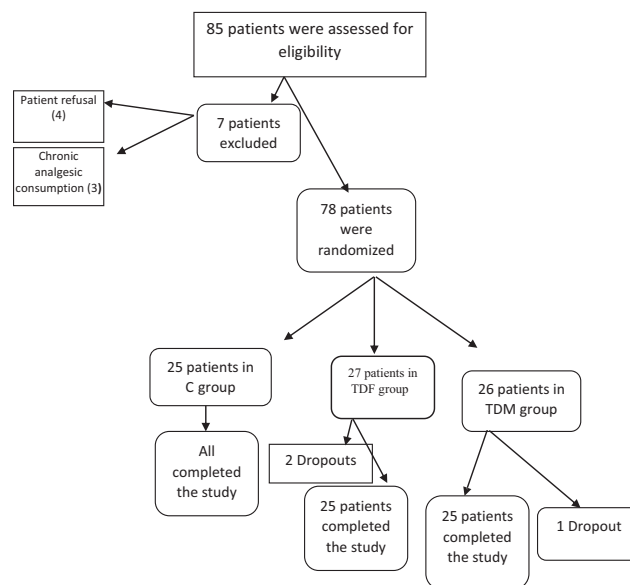

Figure 2 Flowchart of patients (study design).

study medication after randomization, 75 patients completed the study (25 patients for each group) and their data were included in the final analysis (Fig. 2). Seven patients were not included in this study on account of patient's refusal (4 patients) and history of chronic analgesic consumption (3 patients). Three patients were considered as dropouts after initial randomization and were therefore not subjected to further statistical analysis (three patients needed re-exploration on account of the postoperative bleed).

Results of the current study did not show significant difference in the demographic data of the groups of patients regarding age, sex (male to female ratio), body weight, height, ASA physical status and the length of surgery in minutes as shown in Table 3.

No significant differences in HR between the three groups were recorded at any time. There were lower recorded values in the mean heart rate in the TDF and the TDM groups compared to C group, 30 min, 1 h, 2 h and 6 h postoperatively and this was not significant. There was a decrease in the mean heart rate in the TDF group compared to the C and the TDM groups, 12 h postoperatively and this was not significant as shown in Fig. 3.

There was a significant decrease in the mean arterial blood pressure in the TDM group compared to the C and the TDF groups, 30 min, 1 h, 2 h and 6 h postoperatively as shown in Fig. 4.

No significant changes were noted in the SpO_2 between the studied groups throughout the study period ($P > 0.05$).

The sedation score was significantly higher in TDM group compared to the C and the TDF groups, 30 min, 1, 2, and 6 h postoperatively as shown in Fig. 5.

Table 3 The demographic data.

Variables	C group (n = 25)	TDF group (n = 25)	TDM group (n = 25)	p-value
Age (yr.)	43.56 ± 5.7	42.6 ± 4.62	44.56 ± 3.4	0.83
Sex (M/F)	15/10	14/11	13/12	0.21
Weight (kg)	77.18 ± 4.2	76.32 ± 5.9	78.4 ± 3.1	0.57
Height (cm)	166.56 ± 5. 4	170.71 ± 4	168.6 ± 5.2	0.2
ASA (I/II)	11/14	9/16	7/18	0.85
Duration of anesthesia (min)	112.5 ± 6.5	112.8 ± 6.8	111.7 ± 5.2	0.51

Data are presented as mean ± SD. ASA: American Society of Anesthesiologists.

$P > 0.05$ was considered statistically non-significant between the 3 groups.
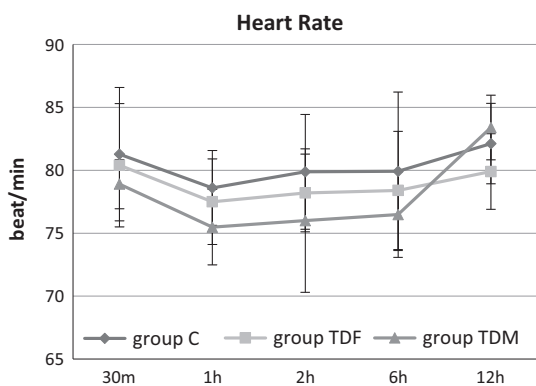
Lines are mean heart rate and error bars are SD.

Figure 3 The heart rate changes (beats/min). Lines are mean heart rate and error bars are SD.
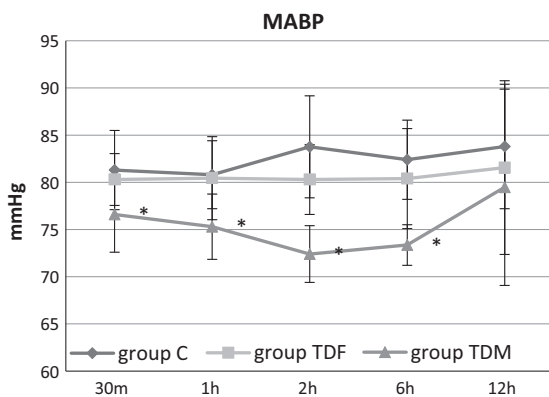
* denotes significant difference.
Lines are mean MABP and error bars are SD.

Figure 4 The mean arterial blood pressure (mmHg).

The middle black solid line represents the median RSS score, and the upper and lower margins of the boxes are IQR and the whiskers are minimum and maximum.

There were significant lower recorded values in visual analog scale in the TDF group and TDM group in comparison with C group, 30 min, 1, 2 and 6 h postoperatively. Pain score was lower in the TDF group compared to the C and the TDM

groups, 12 h postoperatively and this was not significant as shown in Fig. 6.

The middle black solid line represents the median VAS score, the upper and lower margins of the boxes are IQR and the whiskers are minimum and maximum.

Regarding side effects in our study, all cases of the 3 groups were hemodynamically stable, no patient developed hypoxia and there were no reported intraoperative complications interfering with the course of surgery or interrupting the surgeons. Two patients in the C group suffered from nausea ($p = 0.08$). In the TDF group, nausea and vomiting occurred only in 25% of cases ($n = 6/25$) ($p = 0.01$) in spite of the fact that preoperative granisetron (1 mg IV) was given as a prophylactic antiemetic and there were no reported cases of erythema, respiratory depression or pruritus. In the TDM group, two patients were dizzy ($p = 0.08$).

There was significant difference postoperatively between the TDF and the TDM groups in comparison with C group as regards the time for 1st rescue analgesic (minutes) postop, the total pethidine requirements (mg) 12 h postop, the serum cortisol (µg/dl) 2 h postop and the patient's satisfaction score. Intraoperative bleeding measured by bleeding scale was statistically significantly less in the TDM group than in the C and the TDF groups. The surgeon's satisfaction score was significantly higher in the TDM group compared to the C and the TDF groups as shown in Table 4.

4. Discussion

In the present study, there was an overall significant reduction in the VAS score in the TDF and TDM groups when compared with the C group in the 1st 6 h postoperatively. Even in the next 6 h where there was no significant reduction of the VAS, it was still lower in the TDF group than the C and TDM groups. This reduction in the VAS score was associated with significant delay in the postoperative time for 1st rescue analgesic (minutes), significant reduction in the postoperative total pethidine requirements (mg) 12 h postoperatively, significant reduction in the 2 h postoperative serum cortisol (µg/dl) and the significant increase in the postoperative patient's satisfaction score as compared with the group C.

Also, this study revealed that the sedation score was significantly higher in the TDM group compared to the C and the TDF groups, 30 min, 1, 2, and 6 h postoperatively.

These results are in agreement with the findings of Radwan et al. (2010) who reported that pre-emptive oral dose of 6 mg of melatonin reduced the pain scores and pethidine
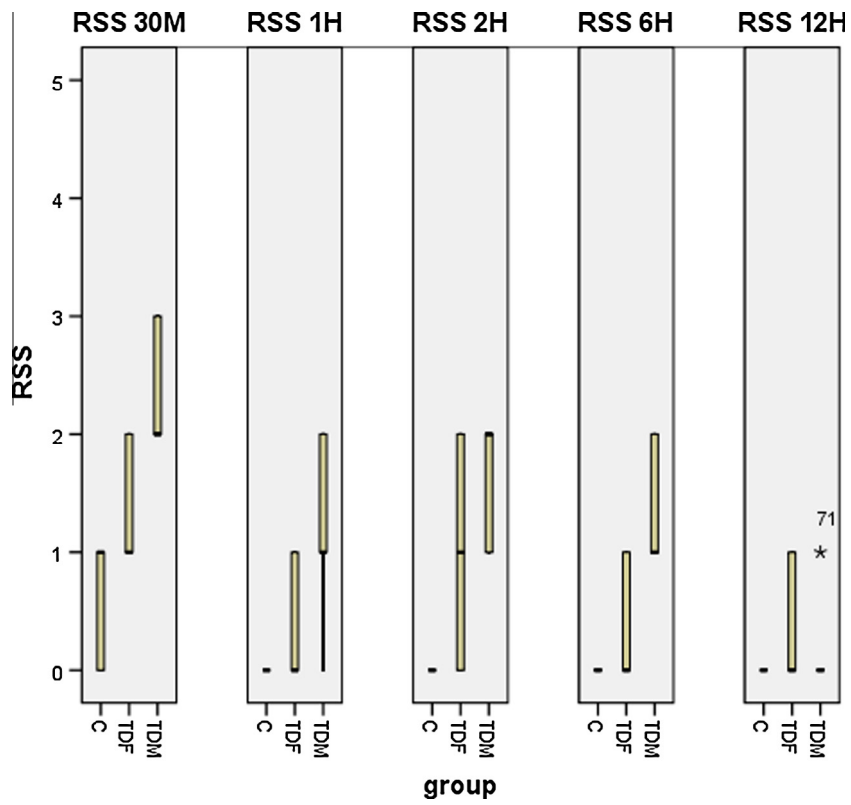
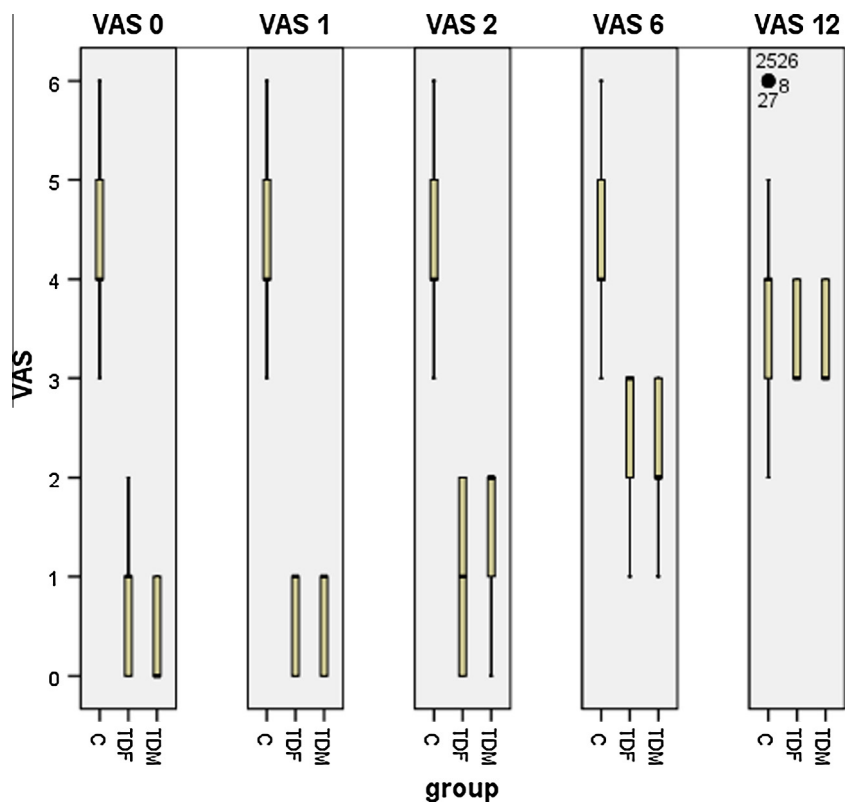**Figure 5**   Sedation score (Ramsay sedation score).

Figure 6   Visual analog scale (VAS).

Table 4 Postoperative data.

Postoperative data	C group ($n = 25$)	TDF group ($n = 25$)	TDM group ($n = 25$)	p-value
Time for 1st rescue analgesic (minutes) postop.	29 .8 ± 2.71[†]	231.5 ± 5. 81	212.5 ± 3.3	<0.001[*]
Total pethidine requirements (mg) 12 h postop.	120.8 ± 7.54[†]	56.32 ± 6.8	60.92 ± 6.4	<0.001[*]
Serum cortisol 2 h postop. (µg/dl).	31.36 ± 4.64[†]	21.34 ± 3.3	21.2 ± 3.9	<0.001[*]
Patient's satisfaction score	2 (2–2.5)[†]	6 (5–6)	6 (5–6)	<0.001[*]
Intraoperative bleeding (0–2)	15(60%)	17(68%)	20(80%)[‡]	<0.001[*]
Surgeon's satisfaction score	4 (4–5)	4 (4–5)	7 (6–7)[‡]	<0.001[*]

Data are presented as mean (SD) or median (interquartile range). [*] Denotes significant difference.
[*] $P < 0.001$ is considered statistically significant between the 3 groups.
[†] $P < 0.001$ was considered statistically significant between groups II and III and group I.
[‡] $P < 0.001$ was considered statistically significant between groups I and II and group III.

requirements in the first postoperative 24 h in patients undergoing abdominal surgery [31].

Borazaa et al. (2010) also reported that preoperative oral melatonin 6 mg, the night before and 1 h before surgery, decreased pain scores and tramadol consumption and enhanced sleep quality and sedation scores during the postoperative period in patients undergoing elective prostatectomy [32].

These results were consistent with Caumo et al. (2010) who found that 5 mg oral melatonin, the night before and 1 h before surgery in patients undergoing abdominal hysterectomy, decreased pain and anxiety during the first 24 h after surgery [33].

These results are in agreement with the findings of Sevarino et al. (1992), who compared TDF in two different delivery rates 25 µg/h and 50 µg/h with placebo for postoperative analgesia after abdominal gynecologic surgery (the patches were applied one hour before surgery and removed after 72 h) and found that there was only a significant reduction in the rescue analgesia in the TDF group with a delivery rate of 50 µg/h [13].

Our results were consistent with the findings of Kilbride et al. (1994), who compared TDF with delivery rate of 50 µg/h applied six hours before surgery and removed after 72 h with placebo for the management of post-hemorrhoidectomy pain and found that there was significant reduction in the pain intensity and rescue analgesia in the TDF group when compared with the placebo group [34].

These results were partially consistent with the findings of Sandler et al. (1994), who compared TDF in two different delivery rates 50 µg/h and 75 µg/h with placebo for postoperative analgesia after abdominal hysterectomy (the patch was applied two hours before surgery and removed after 72 h) and found that there was significant reduction in the pain intensity and rescue analgesia in the TDF group with delivery rate of 75 µg/h when compared with the placebo group while in the TDF group with delivery rate of 50 µg/h there was only a significant reduction in rescue analgesic consumption when compared with the placebo group [35].

Our results were supported with the findings of Siafaka et al. (2004), who studied pharmacokinetic profile and efficacy of a transdermal fentanyl delivery system 50 µg/h for Acute Postoperative Pain after Intra-abdominal Gynecologic Surgery for Cancer and found that Transdermal fentanyl provided effective analgesia for acute postoperative pain and the VAS pain scores were consistently better in the fentanyl group compared with the placebo group; 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 (pain control was supplemented with a nonopioid drug, bupivacaine 0.125–0.25%, administered through an epidural catheter via patient-controlled epidural analgesia) [9].

These results are in agreement with the findings of Minville et al. (2008), who compared the preoperative transdermal fentanyl patch (TFP) 50 µg/h applied approximately 10 h before induction of general anesthesia for the postoperative pain management of patients undergoing primary total hip arthroplasty with patient-controlled analgesia (PCA) and found that Preoperative TFP application decreases pain scores and morphine consumption in the postanesthesia care unit (PACU) [36].

Our results were supported with the findings of Lauretti et al. (2009), who reported that TDF 25 µg/h placed 10 h preoperatively and removed 24 h later combined with IV ketoprofen was effective in controlling postoperative pain after posterior laminectomy [37].

These results are in agreement with the findings of Barrera et al. (2009), who concluded that transdermal fentanyl provided effective postoperative analgesia and reduced analgesic consumption in patients undergoing dorsal and lumbar spine arthrodesis [38].

Our results were supported with the findings of Amr et al. (2012) who found that there was significant reduction in the VAS scores and rescue analgesia in the TDF group with a delivery rate of 50 µg/h when compared with the placebo group during transdermal administration of fentanyl 50 µg/h 10 h preoperatively for postoperative pain relief after major abdominal surgery. Sedation occurred only in the 1st 8 h postoperatively and it was only in the form of drowsiness that was resolved spontaneously [39].

These results were supported by the study of Ismail and Mowafi (2009) who concluded that oral melatonin premedication (10 mg tablet) for patients undergoing cataract surgery under topical anesthesia provided anxiolytic effects, enhanced analgesia and decreased IOP resulting in good operating conditions (22).

These results were partially consistent with Khezri and Merate (2013) who reported that sublingual melatonin 3 mg premedication (60 min before surgery) for patients undergoing cataract surgery under topical anesthesia reduced the anxiety scores in patients and they could not demonstrate that melatonin has a decreasing effect on pain scores [40].

The significant increase in the postoperative patient's satisfaction score in TDM group as compared with group C could be a consequence of melatonin's effects on pain and anxiety which enhance sleep wake cycle disruption in stressful situations such as surgeries, providing better recovery quality [32]. Clinical trials on the effect of melatonin on delirium in hip fracture patients are going on. Melatonin has been used successfully to treat and prevent post-operative delirium [40].

No significant differences in HR between the three groups were recorded at any time. There was a significant decrease in the mean arterial blood pressure in the TDM group compared to the C and the TDF groups, 30 min, 1 h, 2 h and 6 h postoperatively.

These results were supported by the study of Ismail and Mowafi (2009) who found that the mean arterial pressure was decreased after melatonin pre-medication and extended to the early post-operative period. This mild hypotensive effect of melatonin may be beneficial in elderly patients, particularly those at cardiovascular risk [22].

Previous studies showed that melatonin could decrease MAP in healthy women [41] and men [42]. The mechanism of action of melatonin on circulation is complex and unclear. Melatonin may bind to specific melatonin receptors in the blood vessels, interfering with the vascular response to catecholamine [43]. Furthermore, melatonin may interfere with the peripheral and central autonomic system, causing a reduction in adrenergic outflow and catecholamines levels [44]. In addition, it may induce relaxation of the smooth muscle of the arterial walls via increasing nitric oxide availability [45,46].

Intraoperative bleeding was significantly less in TDM group as compared to C and TDF groups. Intraoperative hypotension effectively decreases surgical blood loss and improves surgical field exposure which is essential for spinal surgeries. This result explained significant increase in the surgeon's satisfaction score in the TDM group compared to the C and the TDF groups.

As regards the TDF, these results are in agreement with the findings of Amr et al. (2012) who reported that there were no statistically significant differences between the TDF and control (C) groups in the hemodynamic parameters [systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR)] throughout the period of the study [39].

As regards side effects in our study, all cases of the 3 groups were hemodynamically stable, no patient developed hypoxia and there were no reported intraoperative complications interfering with the course of surgery or interrupting the surgeons. Two patients in the C group suffered from nausea ($p = 0.08$). In the TDF group, nausea and vomiting occurred only in 25% of cases ($n = 6/25$) ($p = 0.01$) in spite of the fact that preoperative granisetron (1 mg IV) was given as a prophylactic antiemetic and there were no reported cases of erythema, respiratory depression or pruritus. In the TDM group, two patients were dizzy ($p = 0.08$).

These results are in agreement with the findings of Amr et al. (2012) who reported that nausea and vomiting occurred only in 32% of cases (16/50 patients) during transdermal administration of fentanyl 50 μg/h 10 h preoperatively for postoperative pain relief after major abdominal surgery [39].

In the TDF group with delivery rate of 75 μg/h the incidences of respiratory depression, sedation and nausea/vomiting were 11%, 22% and 83% respectively [47]. Another study showed that, the incidence of respiratory depression

was higher in the TDF group with delivery rate of 75 μg/h (15%) than in the TDF group with delivery rate of 50 μg/h [35]. The results of our study were partially consistent with Minville et al. (2008) who reported that in the TDF group (15 patients) with delivery rate of 50 μg/h, there were no reported cases of sedation, respiratory depression or erythema; pruritus occurred in one patient and nausea/vomiting occurred in 7 patients; and the only prominent adverse event was the occurrence of local erythema in 30% of patients received transdermal fentanyl [36].

Regarding adverse effects in patients who received TDM, patients were more sedated ($P < 0.05$) and two patients were dizzy ($p = 0.08$). These results were nearly similar to the results proved by Ismail and Mowafi (2009) who found that one patient in their melatonin group ($n = 20$) complained of dizziness [22].

5. Limitations of the study

Our study presented several limitations. First, the results did not allow for an evaluation of the effectiveness of TDF or TDM in all types of surgery. The second limitation was the small sample size preventing achievement safety conclusions. The third limitation of our study is that we did not measure fentanyl and melatonin plasma levels so the interaction between both agents and endogenous melatonin could not be assessed.

6. Conclusion

Transdermal administration of fentanyl 50 μg/h or transdermal therapeutic system containing 7 mg of melatonin 2 h preoperatively was an effective, simple, noninvasive, and convenient technique and a safe adjuvant for acute pain after lumber laminectomy. TDF and TDM allowed delivery of a potent analgesic agent providing a stable serum concentration for an extended period of time with acceptable minimal side effects.

7. Recommendations

The use of the TDF or TDM patches as a component of a multimodal analgesic system (i.e. in conjunction with regional blocks, a non-steroidal anti-inflammatory drug (NSAID), an acetaminophen or an α-agonist) may provide an effective postoperative analgesic regimen.

Clinical trial registration: ClinicalTrials.gov Identifier: NCT02726126

Conflict of interest

None.

References

[1] Melzack R. Psychological aspects of pain: implications for neural blockade. In: Cousins MJ, Bridenbaugh PO, editors. Neural blockade in clinical anesthesia and management of pain. Philadelphia: J.B. Lippincott; 1989. p. 845–60.

[2] Desborough JM. The stress response to trauma and surgery. Br J Anesth 2000;85:109–17.

[3] Carli F, Mayo N, Klubien K, et al. Epidural analgesia enhances functional exercise capacity and health-related quality of life after colonic surgery: results of a randomized trial. Anesthesiology 2002;97:540.

[4] Kissin I. Preemptive analgesia. Anesthesiology 2000;93:1138–43.

[5] McCaffery M, Ferrell B. Nurses' knowledge of pain assessment and management: how much progress have we made? J Pain Symptom Manage 1997;14(3):175–88.

[6] Kücükakin B, Lykkesfeldt J, Nielsen HJ, Reiter RJ, Rosenberg J, Gögenur I. Utility of melatonin to treat surgical stress after major vascular surgery–a safety study. J Pineal Res 2008;44:426–31.

[7] Berner B, John VA. Pharmacokinetic characterization of transdermal delivery systems. Clin Pharmacokinet 1994;26:121–34.

[8] Michaels AS, Chandrasekaran SK, Shaw JE. Drug permeation through human skin: theory and in vitro experimental measurement. Am Inst Chem Eng J 1975;21:985–96.

[9] Siafaka I, Rellia P, Argyra E, Iakovidou N, Sykiotis C, Vadalouka A. Pharmacokinetic profile and efficacy of a fentanyl transdermal delivery system for acute postoperative pain after intra-abdominal gynecologic surgery for cancer. Pain Practice 2004;4(2):98–104.

[10] Muijsers RBR, Wagstaff AJ. Transdermal fentanyl. An updated review of its pharmacological properties and therapeutic efficacy in chronic cancer pain control. Drugs 2001;61:2289–307.

[11] McCartney CJ, Sinha A, Katz J. A qualitative systematic review of the role of N-methyl-D-aspartate receptor antagonists in preventive analgesia. Anesth Analg 2004;98:1385–400.

[12] Plezia PM, Kramer TH, Linford J, Hameroff SR. Transdermal fentanyl: pharmacokinetics and preliminary clinical evaluation. Pharmacotherapy 1989;9:2–9.

[13] Sevarino FB, Naulty JS, Sinatra R, et al. Transdermal fentanyl for postoperative pain management in patients recovering from abdominal gynecologic surgery. Anesthesiology 1992;77(3):463–6.

[14] Bromage PR, Shibata HR, Willoughby HW. Influence of prolonged epidural blockade on blood sugar and cortisol responses to operations upon the upper part of the abdomen and thorax. Surg Gynaecol Obstetr 1971;21:330–5.

[15] Donner B, Zenz M, Tryba M, et al. Fentanyl TTS zur postoperativen Schmerztherapie. A neue Alternative? Anesthetist 1993;42(5):309–15.

[16] Arendt J. In melatonin and the mammalian pineal gland. London: Chapman & Hall; 1995, p. 42, 207.

[17] Barrenetxe J, Delagrange P, Martinez JA. J Physiol Biochem 2004;60:61.

[18] Waldhauser F, Waldhauser M, Lieberman HR, Deng MH, Lynch HJ, Wurtman R. J Neuroendocrinol 1984;39:307–13.

[19] Lee B, Parrott K, Ayres J, Sack R. Res Commun Mol Path Pharmacol 1994;85(3):337–46.

[20] Kücükakin B. Modification of surgical stress response by perioperative melatonin administration. Dan Med Bull 2010;57(5):B4144.

[21] Zahn PK, Lansmann T, Berger E, Speckmann E, Musshoff U. Gene expression and functional characterization of melatonin receptors in the spinal cord of the rat: implications for pain modulation. J Pineal Res 2003;35:24–31.

[22] Ismail SA, Mowafi HA. Melatonin provides anxiolysis, enhances analgesia, decreases intraocular pressure, and promotes better operating conditions during cataract surgery under topical anesthesia. Anesth Analg 2009;108:1146–51.

[23] Yu CX, Zhu CB, Xu SF, Cao XD, Wu GC. Selective MT2 melatonin receptor antagonist blocks melatonininduced antinociception in rats. Neurosci Lett 2000;282:161–4.

[24] Benyahia N-M, Breebaart MB, Sermeus L, Vercauteren M. Regional analgesia techniques for spine surgery: a review with special reference to scoliosis fusion. J Spine 2015;4:208. http://dx.doi.org/10.4172/2165-7939.1000208.

[25] Rahimzadeh P, Faiz SHR, Alimian M, Mohammadian Erdi A. Remifentanil versus dexmedtomidine for posterior spinal fusion surgery. Med J Islam Repub Iran 2015;29:215 [6 June].

[26] Rutberg H, Hakanson E, Anderberg L, Jorfeldt L, Martensson J, Schildt B. Effects of the extradural administration of morphine, or bupivacaine, on the endocrine response to upper abdominal surgery. Br J Anesth 1984;56:233–7.

[27] Hjortso N-C, Christensen NJ, Andersen T, Kehlet H. Effects of the extradural administration of local anesthetic agents and morphine on the urinary excretion of cortisol, catecholamines, and nitrogen following abdominal surgery. Br J Anesth 1985;57:400–6.

[28] Riker RR, Picard JT, Fraser GL. Prospective evaluation of the sedation–agitation scale for adult critically ill patients. Crit Care Med 1999;27:1325–9.

[29] Streiner DL, Norman GR. Scaling responses. In: Streiner DL, Norman GR, editors. Health measurement scales: a practical guide to their development and use. Oxford: Oxford University Press; 1995. p. 28–53.

[30] Rathjen T, Bockmuhl U, Greim CA. Modern anesthesiologic concepts supporting paranasal sinus surgery. Laryngorhinootologie 2006;85:20–3.

[31] Radwan K, Youssef M, El-Tawdy A, Zeidan M, Kamal N. Melatonin versus Gabapentin. A comparative study of preemptive medications. Internet J Anesthesiol 2010;23(1) [DOI:10.5580/265See more at: http://www.ispub.com/journal/theinternetjournalofanesthesiology/volume-23-number-1/melatoninversusgabapentinacomparativestudyaspreemptivemedications.html#sthash.tGPya1vY.dpuf].

[32] Borazaa H, Tuncer S, Yalcin N, Erol A, Otelcioglu S. Effects of preoperative oral melatonin premedication on postoperative analgesia, sleep quality and sedation in patients undergoing elective prostatectomy: a randomized clinical trial. J Aesth 2010;24:155–60.

[33] Caumo W, Torres F, Moreira Jr NL, Auzani JA, Monteiro CA, Londero G, et al. The clinical impact of pre-operative melatonin on post-operative outcomes in patients undergoing abdominal hysterectomy. Anesth Analg 2007;105:1263–71.

[34] Kilbride M, Morse M, Senagore A. Transdermal fentanyl improves management of postoperative hemorrhoidectomy pain. Dis Colon Rectum 1994;37(11):1070–2.

[35] Sandler AN, Baxter AD, Katz J, et al. A double-blind, placebo-controlled trial of transdermal fentanyl after abdominal hysterectomy. Analgesic, respiratory, and pharmacokinetic effects. Anesthesiology 1994;81:1169–80.

[36] Minville V, Lubrano V, Bounes V, Pianezza A, Rabinowitz A, Gris C, et al. Postoperative analgesia after total hip arthroplasty: patient-controlled analgesia versus transdermal fentanyl patch. J Clin Anesth 2008;20:280–3.

[37] Lauretti GR, Mattos AL, Almeida R, Lima ICPR, Resende CS. Efficacy of fentanyl transdermal delivery system for acute postoperative pain after posterior laminectomy. Post Sess/Euro J Pain 2009;13:S55–S285.

[38] Barrera E, Fernandez-Galinski S, Ferrer MD, Escolano F, Puig M. Postoperative analgesia induced by transdermal fentanyl in dorsal and lumbar spine arthrodesis. Post Sess/Euro J Pain 2009;13:S255–85.

[39] Amr Samy A, Mostafa Mostafa G, Mostafa Mohamed AM. Efficacy and safety of transdermal fentanyl patches on postoperative pain relief after major abdominal surgery. J Am Sci 2012;8(6):417–24.

[40] Khezri MB, Merate H. The effects of melatonin on anxiety and pain scores of patients, intraocular pressure, and operating

conditions during cataract surgery under topical anesthesia. Ind J Ophthalmol 2013;61:319–24.

[41] De Jonghe A, Van Munster BC, van Oosten HE, Goslings JC, Kloen P, van Rees C, et al. The effects of melatonin versus placebo on delirium in hip fracture patients: Study protocol of a randomized, placebocontrolled, double blind trial. BMC Geriatr 2011;11:34.

[42] Cagnacci A, Arangino S, Angiolucci M, Maschio E, Melis GB. Influences of melatonin administration on the circulation of women. Am J Physiol 1998;274:R335–8.

[43] Arangino S, Cagnacci A, Angiolucci M, Vacca AM, Longu G, Volpe A, et al. Effects of melatonin on vascular reactivity, catecholamine levels, and blood pressure in healthy men. Am J Cardiol 1999;83:1417–9.

[44] Sewerynek E. Melatonin and the cardiovascular system. Neuro Endocrinol Lett 2002;23(suppl 1):79–83.

[45] Buijs RM, La Fleur SE, Wortel J, Van Heyningen C, Zuiddam L, Mettenleiter TC, et al. The suprachiasmatic nucleus balances sympathetic and parasympathetic output to peripheral organs through separate preautonomic neurons. J Comp Neurol 2003;464:36–48.

[46] Anwar MM, Meki AR, Rahma HH. Inhibitory effects of melatonin on vascular reactivity: possible role of vasoactive mediators. Comp Biochem Physiol C Toxicol Pharmacol 2001;130:357–67.

[47] Sevarino FB, Paige D, Sinatra RS, et al. Postoperative analgesia with parenteral opioids: does continuous delivery utilizing a transdermal opioid preparation affect analgesic efficacy or patient safety? J Clin Anesth 1997;9(3):173–8.