Effect of chronic preoperative tramadol abuse on paravertebral block following thoracotomy

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Purpose
The aim of the study is to investigate the effect of tramadol abuse on postoperative pain control in patients undergoing paravertebral block following thoracotomy.
Patients and methods
Patients undergoing paravertebral block following thoracotomy were consecutively recruited and were divided into two groups: group T included patients with a history of chronic tramadol abuse and group N included patients with no history of any substance abuse (n=50 in each). Analgesic doses, vital signs, and the visual analog scale were evaluated for the first 3 days postoperatively. Complications and need for additional analgesic agents were also scrutinized.
Results
There were no differences in clinical or surgical details between the groups, but patients in group T needed significantly higher doses of analgesics following surgery ($P<0.05$). This was more so for fentanyl ($P<0.01$). Despite that, visual analog scale scores were higher with less pain control compared with group N ($P<0.05$).
Conclusion
Chronic tramadol abuse has a significant effect on postoperative pain control following thoracotomy. This information can be used to develop better postoperative management plans and refine expectations of both the patients and their health-care providers leading to better clinical outcomes and reduced morbidity.

Keywords:
paravertebral block, postoperative pain, thoracotomy, tramadol abuse

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Introduction

An increasing number of patients with a history of chronic opioid use requires routine surgery [1]. It is therefore of paramount importance for medical-care providers to be aware of how this will affect perioperative care and overall outcome. Tramadol is a centrally acting analgesic structurally related to codeine and morphine which exerts its nociceptive effect by acting as an agonist of μ-opioid receptors [2]. While it is a relatively safe analgesic, there is a high incidence of tramadol abuse with some reports of up to 69 per thousand persons per year and a dependence rate of 6.9 per thousand persons per year [1]. Numerous studies have investigated the factors associated with discontinuation and prolonged use of opioids postoperatively in patients with a history of perioperative opioid use [3,4] and there is evidence indicating that chronic opioid use is a preoperative risk factor associated with poor postoperative outcomes [5,6]. There is little information regarding how chronic opioid abuse may affect postoperative pain control. Gaining insights on this will have great clinical implications for both the patients and their health-care providers and help develop better management protocols tailored specifically for those patients.

Thoracotomy is marked by severe postoperative pain which can lead to depression of respiratory function and can result in complications such as pneumonia and delayed recovery [7–9]. This is aggravated further in patients with coexisting cardiac and respiratory diseases as well as in the elderly and malnourished patients [10]. Thoracic paravertebral block (PVB) is a regional technique that was developed to improve postoperative pain in those patients [11]. It involves continuous infusion of a local anesthetic with or without opioids into a catheter inserted into the paravertebral space [12]. This produces unilateral somatic and sympathetic blocks [13] with subsequent alleviation of pain. There is no data regarding how this can be affected by chronic preoperative opioid use.

The purpose of this study was to evaluate the effect of chronic tramadol abuse on the efficacy of PVB in controlling pain after thoracotomy. We aimed to find out whether prolonged use of tramadol prior to surgery would be associated with poorer pain control and/or higher risk of anesthesia-related adverse effects.

Patients and methods

Study design and participants

This is a prospective comparative observational study that included 100 consecutive patients who underwent thoracotomy, for Bullectomy, Pneumonectomy, or Lobectomy in Kasr Al-Aini Hospital between 2016 and 2018. All the patients had thoracic surgery via a posterolateral thoracotomy incision.

The patients were divided into two groups:

Group T: included 50 patients with a history of tramadol abuse for at least 12 months prior to the procedure. Abuse was defined in accordance with the *Diagnostic and Statistical Manual of Mental Disorders* IV as a maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by social, interpersonal, and other problems related to substance use occurring within a 12-month period [14]. Patients with a history of any other concomitant drug abuse were not included.

Group N: included 50 patients with no history of any substance abuse.

The inclusion and exclusion criteria were identical in both groups.

Inclusion criteria: (a) age at surgery of 20–60 years, (b) American Society of Anesthesiologist physical status I–III [15], (c) platelet count more than or equal to 100 000/mm^3, (d) prothrombin concentration more than 70%, (e) serum creatinine level less than or equal to 2.0 mg/dl, and (f) forced expiratory volume in 1 s more than or equal to 70%.

Exclusion criteria: (a) lack of patient consent, (b) patients with serious cardiac complications, (c) patients with a history of allergy to local anesthetics or narcotics, (d) patients with contraindication to regional techniques, (e) history of ipsilateral thoracotomy, (f) patients with a history tuberculosis or at risk of intrathoracic adhesion, (g) patients with interstitial pneumonia, pulmonary fibrosis, or severe pulmonary emphysema, (h) patients with a need for an additional incision, (i) patients previously subjected to radiotherapy involving the thoracic wall/cavity, (j) patients with active infectious disease, liver cirrhosis, or renal failure, (k) pregnant women, and (l) mentally challenged patients.

The study was approved by the local ethics committee and informed written consent was obtained from each patient.

Anesthetic technique

Prior to surgery, all patients were evaluated clinically, biochemically, and radiologically including spirometry. The patients were all fasting for at least 8 h prior to the surgery and were given 10 mg oral diazepam and 50 mg ranitidine the night before. None of the patients were given any narcotics.

When the patients arrived at the operation room, all the preoperative vital signs were checked and the patient was monitored by a 5-lead ECG, IABP, SpO2%, capnometry, and arterial blood gases were measured. Induction was performed by injecting fentanyl 2 μg/kg intravenous, propofol 2 mg/kg, and atracurium besylate 0.5 mg/kg. Lidocaine 1.5 mg/kg was given 90 s prior to intubation. Patients were then intubated with double lumen/single ETT and anesthesia was maintained with oxygen, isoflurane and atracurium besylate 0.5 mg/kg/h, and mechanical ventilation.

After skin closure, while the patients were in the lateral position, skin preparation was performed and a 16-G epidural catheter was inserted via a 16-G epidural needle at the T5–T9 intervertebral space. Infusion of 2 ml of 1% lidocaine hydrochloride was done as a test dose. This was followed by recording of baseline hemodynamic vitals. When the absence of any adverse effects was confirmed, 10 ml of 2% lidocaine was infused, followed by infusion of 10 ml/h of 0.25% bupivacaine and 4 μg/ml fentanyl solution through an infuser pump.

At the end of the surgery, all patients were given assisted ventilation till spontaneous respiratory attempts, and then reversed with 50 μg/kg of neostigmine and 10 μg/kg atropine. They were then extubated and transferred to the surgical ICU where continuous oxygen was given at 4 l/min for the next 72 h.

Postoperative assessment

The rate of infusion in the paravertebral catheter was tailored according to patient response and the total daily doses of bupivacaine and fentanyl used

throughout the first 3 days postoperatively were recorded.

Pain was assessed using the visual analog scale (VAS; 0=no pain;10=worst imaginable pain) at 30 min, 12, and 24 h after administrating the drug. VAS score of 0 was taken as complete analgesia and a score less than 4 as effective analgesia. Whenever VAS was more than or equal to 4, the patients were given intravenous fentanyl 30 μg top-up dose.

If the patient was still in pain, additional analgesia with regular NSAIDs were given. The VAS scores as well as the number of times additional fentanyl doses was administrated during the first 3 days were recorded.

Length of inpatient stay and any complications or side effects such as respiratory depression, hemodynamic changes like bradycardia, hypotension, nausea, and vomiting or urinary retention were recorded. Significant changes were defined as (a) hypotension: drop of systolic blood pressure to less than 90 mmHg or changes in blood pressure exceeding 20% of the baseline on two consecutive measurements taken at 5-min intervals. (b) Bradycardia: drop of heart rate to less than 50 beats/min or changes in heart rate exceeding 20% of the baseline persisting for more than 30 s. (c) Hypoxemia: a decrease in oxygen saturation to less than 92% persisting for 30 s.

Statistical analysis

Data collected were collected by ICU doctors and nurses as well lab technicians who were blinded to group allocation. Descriptive statistical analysis was used. The *t* test was used for comparison of continuous variables between the two groups and the c^2 test or Fisher's exact test was used for categorical variables. A two-sided *P* less than 0.05 was considered significant for these comparisons, with 95% confidence intervals.

Results

The average duration of tramadol use was 6.3±2.6 years and the mean total daily dose used was 514.7 ±112.3 mg. The most frequent dose range used was 400–500 mg (47% of patients).

As demonstrated in Table 1, no significant differences were found between the two groups and they were comparable in terms of demographic and clinical characteristics.

There was also no difference in surgical procedure details or hemodynamic stability during the surgery (Table 2).

Table 1 Patient characteristics

Variables	Group T (*N*=50)	Group N (*N*=50)
Age (year, mean±SD)	42.9±11.2	49.2±10.6
Height (cm, mean±SD)	173.1±8.6	169.9±9.4
Weight (kg, mean±SD)	81.4±12.2	73.8±10.1
Sex (*n* of *M*)	16	17
Smokers (%)	49	51

Table 2 Surgical characteristics in each group (mean±SD)

Variables	Group T (*N*=50)	Group N (*N*=50)
Duration of anesthesia (min)	263.9±47.2	271.3±39.1
Operation time (min)	203.1±46.2	199.8±46.2
Blood loss (ml)	104.2±95.7	99.8±81.3
Length of skin incision (cm)	15.6±1.9	15.2±3.2
Average heart rate/min	92.3±6.2	91.7±7.1
Average blood pressure (mmHg)	122.4±7.8	121.8±9.1
Average O_2 saturation (%)	99.3±0.6	99.1±0.7

Table 3 Incidence of adverse effects related to anesthetic agents or the procedure

Adverse event	Group T (*N*=50)	Group N (*N*=50)
Hypoxemia	6	4
Hypotension	2	1
Bradycardia	0	0
Cough and dyspnea*	12	2
Urinary retention	2	1
Nausea and vomiting	2	0

**P* value less than 0.05

Table 4 Total daily doses of analgesics administrated (mean ±SD)

Variables	Group T (*N*=25)	Group N (*N*=25)	*P* value
Bupivacaine dose (mg)*	931±102	593±93	0.029
Fentanyl dose (μg)**	1450±340	700±200	0.0036

**P* value less than 0.05. ***P* value less than 0.01.

Patients in the tramadol group had a significantly higher incidence of postoperative dyspnea and cough (Table 3). This was the only difference in reported adverse events related to sedation or the procedure between the two groups.

As shown in Table 4, the total daily doses of all analgesics administrated through the paravertebral catheter were significantly higher in the tramadol group ($P<0.05$). This was particularly evident in the dose of fentanyl ($P<0.01$).

The frequency of administration of additional analgesia is summarized in Table 5. The number of times the patients needed to take additional analgesia to control

Table 5 Frequency of additional drug administration in the first 3 days and total length of stay (mean±SD)

Variables	Group T (*N*=25)	Group N (*N*=25)	*P* value
Operative day (number)**	4.6±2.1	1.5±1.3	0.0004
Postoperative day 1 (number)**	3.9±1.4	1.3±1.1	0.0016
Postoperative day 2 (number)**	3.8±1.4	1.3±0.9	0.0019
Total length of stay (days)*	8.5±9.9	5.3±1.4	0.029

**P* value less than 0.05. ***P* value less than 0.01.

Table 6 Pain score (visual analog scale) in the two groups of patients (mean±SD)

Pain score	Group T (*N*=25)	Group N (*N*=25)	*P* value
Operative day*	3.2±1.2	1.0±0.7	0.023
Postoperative day 1*	3.1±0.9	1.2±0.4	0.036
Postoperative day 2*	3.1±0.7	1.2±0.1	0.040

**P* value less than 0.05.

their pain was much higher in the tramadol group ($P<0.05$). In addition, the total length of stay was significantly longer for the patients with tramadol abuse ($P<0.05$).

VAS scores in both groups was less than 4 indicating good pain control; however, the scores were significantly higher in the tramadol group ($P<0.05$). This was evident throughout the 3-day follow-up period (Table 6).

Discussion

To the best of our knowledge, our study is the first to investigate the effect of tramadol abuse on postoperative paravertebral analgesia following thoracotomy. We underwent extensive measures to ensure that the only variable affecting the results was tramadol abuse. All the patients were age, sex, and diagnosis matched with no concomitant comorbidity or substance abuse in either group. In addition, all the surgeries were performed by the same surgical team and a single anesthetist performed the PVB and was responsible for postoperative pain analgesia administration.

Patients with preoperative chronic tramadol abuse required much higher doses of analgesics postoperatively compared with others. This was noted throughout the first 3 days and was particularly observed with fentanyl. Despite that, pain control was less. This led to prolongation of hospital stay and increased incidence of cough and dyspnea due to irritation of chest wall nerves and muscles due to pain. The potential mechanisms underlying the link between preoperative opioid use and postoperative pain control are still unclear. There is evidence suggesting that patients taking opioids may experience pain sensitization due to modified peripheral and central pain pathways, the so-called opioid-induced hyperalgesia [16,17]. Further support for this comes from numerous reports indicating that it is very difficult to discontinue opioids postoperatively in patients who chronically use opioids [18]. Tramadol has prominent selectivity for μ-opioid receptors [2]. The M1 metabolite of tramadol, produced by liver O-demethylation, shows a higher affinity for opioid receptors than the parent drug. The rate of production of this M1 derivative (O-desmethyltramadol) is influenced by a polymorphic isoenzyme of the debrisoquine-type, cytochrome P450 2D6 (CYP2D6). Tramadol is actually a racemic mixture of two enantiomers, R (−) and S (+) (3) [2,19]. While both enantiomers inhibit the acetylcholine-mediated response, each one also displays differing affinities for various receptors [2]. The S (+) tramadol has high affinity to μ-opioid receptors and a potent inhibitor of serotonin reuptake, whereas R (−) tramadol is a more potent inhibitor of norepinephrine reuptake [2,19,20]. The complementary and synergistic actions of the two enantiomers improve the analgesic efficacy and tolerability profile of the drug. Tramadol also enhances serotonin reuptake inhibition [2,19] and can inhibit both NMDA-glutamate and gamma-aminobutyric acid-A receptors [2,19,20]. When administrated orally, tramadol demonstrates 68% bioavailability, with peak serum concentrations reached within 2 h. It has a two-compartmental elimination kinetic with a half-life of 5.1 h for tramadol and 9 h for the M1 derivative after a single oral dose of 100 mg. This explains the approximately two-fold accumulation of the parent drug and its M1 derivative that is observed during multiple dose treatments with tramadol [2,19]. All these effects are dose dependent and thus higher doses can potentially lead to more prominent disturbances within the brain circuits.

Both lidocaine and bupivacaine exhibit their anesthetic effect by binding to the intracellular portion of voltage-gated sodium channels and blocking sodium influx into nerve cells, thereby inhibiting the ionic fluxes required for the initiation and conduction of impulses and stabilizing the neuronal membrane [21,22]. Fentanyl on the other hand is an opioid and as such has a mechanism of action similar to tramadol, exerting its

action mainly via the activation of μ-opioid receptors [23]. This may explain why much more doses of fentanyl in particular were required in the tramadol group. It appears that μ-opioid receptors are altered with prolonged use of high doses of tramadol leading to decreased efficacy. All of the patients included in the tramadol group were ingesting high doses of tramadol for at least 2 years. This may have facilitated a 'tramadol-induced cumulative effect' with subsequent modulation of brain circuits and/or alteration of neurotransmission leading to pain sensitization. While chronic smoking may also have played a role as it has been shown to decrease opioid efficacy due to desensitization of acetylcholine receptors [24], we do not believe this had an influence on our results. Both groups included a similar number of chronic smokers.

Another important factor to be considered is the genetic profile of our patients. Two types of CYP2D6 gene carriers responsible for tramadol bioactivation have been identified, the ultra-rapid (UMs) and the extensive (EMs) tramadol metabolizers [25]. The UMs were more sensitive to tramadol with subsequent higher adverse drug events. Both Southern European and Northern African populations are known to have a high proportion of UM gene carriers [25]. This may be a reason for the heightened sensitivity of our patients to the effect of tramadol. Clearly, more research is needed to investigate whether these findings can be applied to the general population.Our study has potential limitations in. First, we relied on self-reported preoperative tramadol use which has the risk of underreporting of the true use in the study population. We could not measure preoperative serum levels of tramadol as this is not available in our hospital. Second, while this is the first study to investigate the effect of tramadol on postoperative pain control after thoracotomy, the number of patients is still relatively small and the follow-up was short, and so subtle differences could have been missed and long-term effects are not available.

Nevertheless, our results have important clinical implications. Postthoracotomy pain is one of the severest forms of pain that can be experienced by a patient. This pain delays ambulation and increases cost of care and hospital stay. Successful postoperative pain management will overcome these problems. Chronic tramadol abuse is a well-recognized problem [1]. Increasing our understanding of the effect of preoperative tramadol abuse on postoperative pain control could have a major impact on preoperative counseling and establish appropriate patient, family, and surgeon expectations. Both the patients and their medical-care providers including the surgeons need to be aware that there is a high likelihood for those patients to experience poorly controlled postoperative pain and require higher doses of analgesia with increased risk of complications related to their use. Furthermore, preoperative tramadol abuse can lengthen the duration of postoperative opioid use. This may lead to dependence or addiction, increase the risk for overdose, and may even increase mortality. Therefore, even though the main line of immediate postoperative pain therapy in those patients still has to be opioids, advanced multimodal analgesic protocols need to be implemented to control pain and prevent addiction. For this, more research is needed and additional stratification according to the types of opioids and usage patterns may be necessary to identify how those patients will respond to postoperative analgesics. This will help establish guidelines that address the need, dose, titration, and maintenance of opioid therapy following surgery. Such an approach will likely improve the quality of care delivered to patients postoperatively.

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Conflicts of interest

There are no conflicts of interest.

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