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RESEARCH ARTICLE

Efficacy, safety, and tolerability of sublingual fentanyl orally disintegrating tablet in the treatment of breakthrough cancer pain: a randomized, double-blind, placebo-controlled study

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Abstract

Background Breakthrough pain (BTP) is an important challenge in treatment and requires a rapid onset of action for pain control. BTP should be adequately controlled with a stable dose of a short-acting oral opioid. So far, no drug is available for the treatment of BTP in cancer patients in Iran, so we designed the first study in Iran to investigate the effect of sublingual fentanyl in relief of pain episodes in these patients.

Objective The purpose of this study was to evaluate the efficacy and safety of sublingual fentanyl in the treatment of breakthrough pain in cancer patients.

Method This study was a randomized double-blind placebo-controlled clinical trial in cancer patients with breakthrough pain (at least 1–4 episodes of acute pain with moderate to severe pain daily) referred to the pain clinic of Akhtar and Masih Daneshvari hospitals in 2019. The study consisted of two stages: 100 patients were selected by simple, non-random sampling and entered the open-label titration phase. The primary efficacy endpoint was the sum of pain intensity difference over 30 min post-administration. Secondary efficacy endpoints included pain intensity difference (PID) and pain relief (PR) throughout the 60-min post-dose assessment period. In the double-blind study, patients were randomly divided into two groups of placebo (n=50) and intervention (sublingual fentanyl tablet) (n=50). For evaluation of efficacy, 10 episodes were treated in each group and the results were recorded by the patient. (Clinical trial registration: IRCT20131124015515N8).

Results A total of 100 patients entered the titration phase, primary efficacy of sublingual fentanyl was 3.5±0.6 and secondary efficacy of sublingual fentanyl (60 min, after treatment) was 0.3±0.6 which was statistically significant. In the titration phase, the treatment success rate was 100%. In the double-blind phase of the study, the pain intensity in multiple episodes showed a significant improvement at 15, 30, 45, and 60 min after drug administration (P=0.0001). The intensity of pain in each episode was significantly decreased compared to the next episode (P=0.0001). The mean frequency of pain episodes in the sublingual fentanyl group showed a significant decrease (P=0.0001). The most common adverse drug events in the titration phase were drowsiness (20%), dizziness (7%), and nausea 4%, and in the double-blind phase only drowsiness (12%). (Cancer Research Center, Shahid Beheshti University of Medical Sciences, Survey).

Conclusion Sublingual fentanyl appears to be effective for patients with rapid-onset analgesia, has short-acting duration, is effective medication, safe, and well tolerated. It is a suitable choice in Iranian patients with chronic cancer-related pain controlled suffering from acute pain episodes related to cancer.

Keywords Sublingual fentanyl · Breakthrough pain · Cancer · Treatment

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Introduction

Cancer pain is highly prevalent, develops early in 30–70% of patients, depending on the clinical conditions [1]. However, some types of cancer pain are more difficult to control. Specific pain syndromes or clinical scenarios, such as breakthrough pain are associated with poor prognoses [2]. Controlling breakthrough pain using strategies separate from chronic cancer pain management techniques brings about favorable results.

The patients with cancer may experience breakthrough pain (BTP) with a transient exacerbation of a chronic and persistent pain, despite receiving chronic opioid treatment [3, 4].

BTP in patients with cancer is known as a sudden increase in pain [5, 6]. In cancer patients with pain, the BTP incidence rate ranges from 40 to 80%, depending on the pain control and definition of BTP [3, 7–10]. The pioneer definition suggests that BTP is a transitory increase in pain over moderate intensity that occurs with a baseline pain of moderate or less than moderate intensity [3]. According to other definitions, a transient exacerbation of pain develops regardless of baseline analgesia [6]. Pain episodes occur without background pain [11], any flame of pain that is subjectively recognizable from background pain [12]. BTP is a transient exacerbation of pain that occurs in the background of controlled pain in patients undergoing chronic opioid treatment [3].

In patients with cancer,BTP is usually associated with functional impairment and psychological distress [13]. In general, BTP is a short, severe pain that is usually characterized by a few episodes per day, lasting from a few minutes to 10 min with an average of 45–60 min. Along with background pain, BTP causes significant anxiety, pain, and suffering that are commonly correlated with depression and low quality of life and mental health [5, 6, 13–16].

Therefore, BTP is an important challenge in cancer treatment and requires a rapid, effective treatment regimen to control pain.

Such pain can be controlled by short-acting and quick-acting medications [16]. These medications are superior to the opioids that are commonly prescribed as a standard to control the pain and can reduce the side effects of opioid consumption, such as nausea, dizziness, and constipation.

Choosing the most appropriate medication and the method of prescribing it is determined by the duration, severity, and time of onset of pain. Opioid drugs have recently become the cornerstone of cancer pain control [17].

Taking transmucosal and sublingual opioids, compared to conventional oral doses, is associated with a noninvasive mechanism of drug absorption, high bioavailability, and rapid pain relief [18, 19]. Sublingual fentanyl tablets lead to the rapid absorption of fentanyl through the sublingual mucosa, which is an effective method for treating BTP, is well-tolerated by patients and improves their quality of life [20–22].

Fentanyl is a quick-acting opioid drug and has clinical benefits that are because of its specific formulation and rapid dissolution, like sublingual tablets, after drug administration [23–27].

Fentanyl is a small, lipophilic drug with μ-receptor agonist properties, prescribed in doses 100–1000 μg and lacks the bitter taste of other opioids [15, 16]. Researchers carried out in vivo studies have revealed that drug absorption in the intestine and oral mucosa is regulated by the physicochemical properties of the drug [22, 28, 29].

Fentanyl is prescribed in a variety of transmucosal and sublingual methods [26, 28]. The sublingual cavity is an alternative method for transmucosal release that demonstrates significant penetration for rapid drug uptake and high bioavailability [30, 31] and is easy to use in patients' self-care.

In patients with BTP, sublingual fentanyl is rapidly absorbed, and the first plasma concentration of fentanyl is detectable about 8 to 11 min after its administration [32, 33].

Because of the low plasma concentrations of the drug, sublingual fentanyl can be of great importance in the treatment of BTP in these patients [34].

Sublingual fentanyl is available in Europe [35] and the United States of America, approved by the Food and Drug Administration. The formulation of sublingual fentanyl tablets prompted the onset of the analgesic effect of the drug and replaced its oral type.

The pharmacodynamics and pharmacokinetics of fentanyl with different formulations have been investigated in several studies [36–39].

Pharmacodynamically speaking, fentanyl is a very strong synthetic opioid with a rapid onset and short effect duration. The lipophilic nature of fentanyl prompts its rapid transfer to the blood-brain barrier [40]. Fentanyl's analgesic potency is 50 to 100 times stronger than morphine [3].

Given the increasing prevalence of various types of cancer, the high prevalence of BTP among cancer patients, the importance of identifying the pharmacokinetics and pharmacodynamics drugs and selecting the appropriate drug with rapid absorption and onset of effect, the benefits of taking sublingual fentanyl, the reduction in consuming opioid drugs and their side effects, the improvement in patients' quality of life, and the reduction in patient's medical costs, BTP should be adequately controlled with a stable dose of a short-acting oral opioid. So far, no drug is available for the treatment of BTP in cancer patients in Iran, so we designed the first study in Iran to investigate the effect of sublingual fentanyl in relief of pain episodes in these patients.

So, this study aimed at examining the effect and safety of sublingual fentanyl in the treatment of BTP in patients with cancer in Iranian population.

Materials and method

This prospective study was a randomized, double-blind, placebo-controlled clinical trial (Clinical trial registration: IRCT20131124015515N8) conducted on patients with cancer (all patients with bone, visceral, and soft tissue cancers were considered) and BTP referred to pain clinics of Akhtar and Masih Daneshvari Hospitals in 2019. Patients who expressed their consent to participate in this study, patients with soft tissue, visceral, and bone malignancies, patients diagnosed with blood or solid malignant tumor, patients aged =<18 years, patients with at least 1–4 episodes pain of daily, patients who were on an oral opioid regimen to control chronic cancer pain at a fixed and similar dose (60–1000 mg of oral morphine or similar opioid daily/30 mg of oral oxycodone daily).

Patients who were unwilling to take part in this study, with a history of taking intrathecal opioid, with a history of mucositis/stomatitis grade 2 and above based on the definition of common terminology criteria for adverse events, [34] and having a condition affecting tolerance or absorption of sublingual fentanyl and patients who were pregnant or breastfeeding, with sleep apnea, active brain metastasis with increased intracranial pressure, chronic pulmonary obstruction, renal or hepatic impairment, significant cardiac arrhythmia due to undiagnosed heart disease, and any non-cancer related BTP, history of misuse of any type of narcotic, opioid and alcohol were excluded .

Before receiving the first dose of the drug, on the first follow-up visit, the patients underwent neurological and physical examinations and clinical tests. Moreover, the patients were instructed to place the tablet under their tongues in the deepest part of the mouth and wait for the drug to dissolve within 30 min, without sucking, swallowing, and chewing.

The patients were asked to refrain from taking pain medication supplements at least 30 min after taking sublingual fentanyl.

All the patients were studied in an open-label titration phase. For titration of drug tolerance, the patients received a trial dose of 100 μg at the pain clinic and were monitored for two hours. It should be noted that during this time there was no need for BTP and both the patient and the researcher were aware of the medication. Furthermore, during the titration phase and in the double-blind phase of monitoring, the patients were monitored at home for drug tolerance through registration in pre-prepared tables that were provided to patients. In the current study, the available doses of sublingual fentanyl were 100 μg and 200 μg.

The patients were then asked to record the baseline pain severity score after the onset of BTP. Afterward, they started taking sublingual fentanyl 100 μg. The patients could take other opioids used in this study if their pain did not satisfactorily relieve within 30 min after the dissolution of the initial dose of the drug. The next BTP usually occurred at least 4 h after receiving sublingual fentanyl or other opioids used in the present study. If the 100 μg dose did not relieve the patient's pain satisfactorily and the side effects of the drug were tolerable, in the subsequent BTP dose of 200 μg sublingual fentanyl might be used. It should be stated that if BTP was relieved with a dose of the drug, the next episode of BTP would be treated with the same dose.

The patients entered the double-blind phase with two consecutive episodes of BTP with the satisfactory improvement of pain within 30 min after the drug administration and not experiencing any unacceptable side effects. If the pain was not sufficiently improved with a higher dose of the drug or some unacceptable side effects occurred, the patient was excluded.

In the double-blind phase, the patients were randomly divided into placebo (placebo tablet, Faran Shimi Pharmaceutical Company, Iran) and intervention (sublingual fentanyl tablet, Faran Shimi Pharmaceutical Company, Iran). groups based on a random number table. Participant and clinical outcomes evaluator are not aware of the code assigned to each of the groups.

The control group took the sublingual fentanyl placebo and 60–600 mg of oral opioid regimen per day/30 mg of oral oxycodone daily for pain relief. The control group was controlled exactly like the intervention group.

At this stage, 10 episodes were treated in each group and the results were recorded by the patients.

During the present study, if the patient did not recover within 30 min after taking the placebo or sublingual fentanyl, he/she could take his/her previous complementary medications to treat any type of BTP. Previous medications could be taken to treat BTP >4 times daily or BTP occurring less than 4 h apart.

The patient was asked to record any side effects of the drug (vomiting, nausea, dizziness, headache, fatigue, constipation, drowsiness, weakness, and fatigue) after taking each dose, including the titration and double-blind phases. At the first (the screening stage), second (the drug titration stage) and fourth (the end of the double-blind phase) visits, oral mucosa was examined and the normal and abnormal findings (ulcer, redness, inflammation, and erosion) were recorded and the cause of such abnormal findings of oral mucosa were checked. The last visit also included physical examinations and clinical tests.

BTP was considered as a transient exacerbation of pain, at least 1–4 episodes of acute pain with moderate to severe intensity daily [3, 4]. The pain severity was measured using the VAS scale (0=no pain, 1–3 mild, 4–6 moderate, and 7–10 severe). The average pain score from baseline at 30 min after receiving the drug to treat the pain episode primary efficacy endpoint and 60 min after receiving medication to treat the pain episode Secondary efficacy endpoints, was considered.

If any additional medications were taken, the patients were asked to record the dose of the medication. Additionally, they

recorded the frequency of daily episodes of pain during the study.

It should be noted that the drug dose segmentation was based on the patients' satisfactory relief of pain within 30 min after the dissolution of 100 μg dose of the drug; however, if the 100 μg dose did not relieve the patient's pain, in the subsequent BTP dose of 200 μg sublingual fentanyl was taken and this dose was taken afterward.

The data were then coded and entered into SPSS version 19. After examining the normal distribution of quantitative data by the Smirnov-Kolmogorov, the quantitative variables were compared using the t-test, Mann-Whitney test and paired t-test. Also, after examining the variance equality data by Sphericity test, it was shown that the data were normally distributed, therefore, mean scores of VAS for the pain severity within two groups in the different episodes were compared using the repeated measurement ANOVA, and the qualitative variables were evaluated by the chi-square test. $P<0.05$ was considered statistically significant in all tests (Fig. 1).

Sample size

According to a Guitart J and colleagues [41] in 2017 at the initiative of formula taking into account the depletion studies, $\alpha= 0.05$,, $\beta= 80\%$,,z- $\alpha=1.96$, z-$\beta=0.85$, $p_1 =100\%$, $p2 = 67\%$ (Power study, 80%), 50 patients in each group were identified.

$$N = \left(z_{\left(1-\frac{\alpha}{2}\right)}2p(1-p) + z(1-\beta)\sqrt{p1(1-p1)} + p2(1-p2/d)\right)^2$$

Ethics

This study was approved by ethics committee of Cancer Research Center of Shahid Beheshti University of Medical Sciences, code number (IR.SBMU.CRC.REC.1398.001) in 29 Jun 2019.

Results

The mean age of the studied population was 47.0±13.3 years and they were in the age range of 21–84-year-old. The mean body mass index (BMI) of the patients was 25.6±3.7 (19.4–38.7) kg/m^2. Sixty patients (60%) were male and 40 patients (40%) were female.

In the titration phase, the treatment success rate was 100%. In the titration phase, in the first episode, 100 patients (100%) received 100 μg of fentanyl; however, due to the insufficient

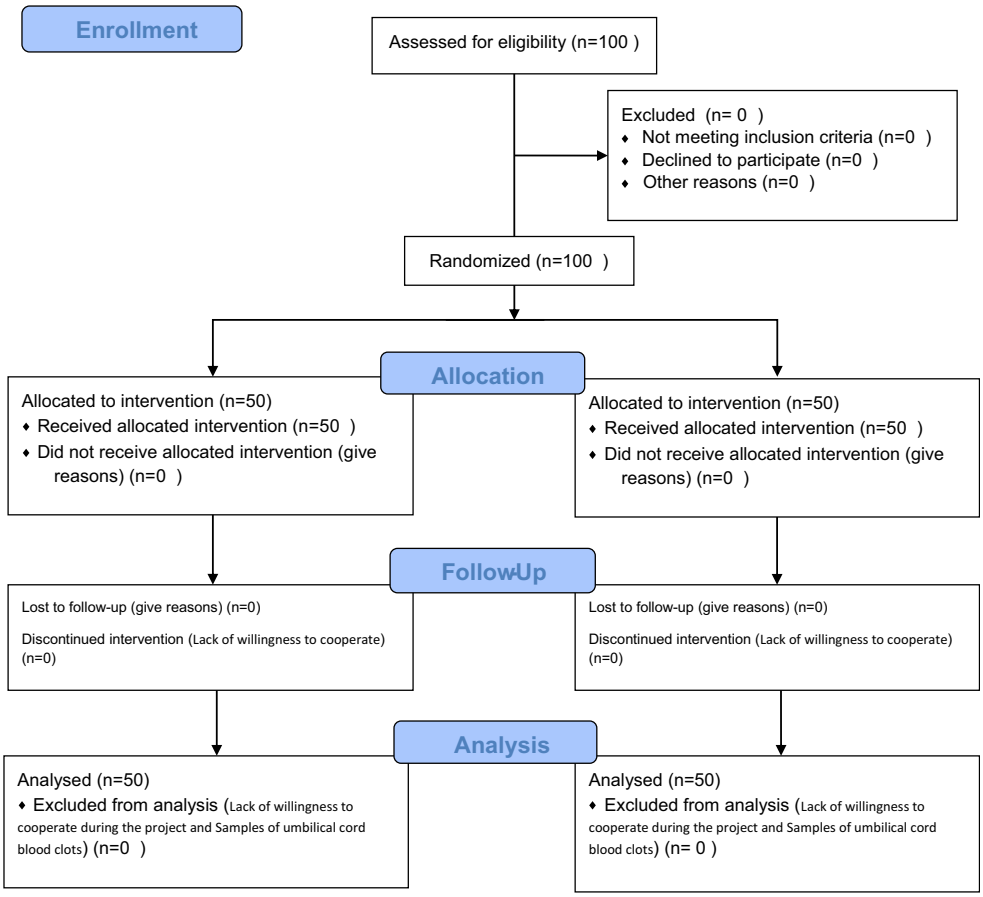

Fig. 1 Consort diagram

improvement, in the second episode, 25 patients (25.0%) took 200 μg of fentanyl and 75 patients (75.0%) continued 100 μg of fentanyl. The effect of fentanyl in relieving the pain was good and the drug had an acceptable effect on pain relief.

Comparing the pain improvement in the two episodes of drug titration phase is shown in Fig. 2, which indicates statistically significant improvements in the two episodes at before, 15 and 30 min after the drug administration (P= 0.0001).

At this stage, 31 patients (31%) showed drug-related side effects (20% drowsiness, 7% dizziness, and 4% nausea). Therefore, the tolerance and safety of the drug were acceptable. Moreover, at this stage, all the patients had normal oral mucosa status.

Then, the patients were randomly assigned to the double-blind study, 50 patients (100%) were in the intervention group and 50 patients (100%) were in the placebo group.

Table 1 compares the demographic data of the two groups.

Comparing the pain relief changes in the first episode of the double-blind phase is shown in Fig. 3, which indicates statistically significant improvements in pain relief changes at 15, 30, 45 and 60 min after the drug administration (P= 0.0001).

Comparing the pain relief changes in the second episode is shown in Fig. 4, which indicates statistically significant improvements in the pain relief at 15, 30, 45 and 60 min after the drug administration (P= 0.0001).

Comparing the pain relief changes 12 h after the first episode between the two groups, i.e., sublingual fentanyl (episode 4) and placebo (episode 6) is shown in Fig. 5, which reveals statistically significant improvements in pain relief at different times, (P= 0.0001).

The primary effect of 100 μg sublingual fentanyl on pain relief was 3.5±0.6 and the secondary effect of 100 μg sublingual fentanyl on pain relief was 0.3±0.6, which was statistically significant (P=0.0001).

Additionally, the primary effect of 200 μg sublingual fentanyl on pain relief was 3.3±0.8 and the secondary effect of 200 μg sublingual fentanyl on pain relief was 0.2±0.4 which was statistically significant (P=0.0001).

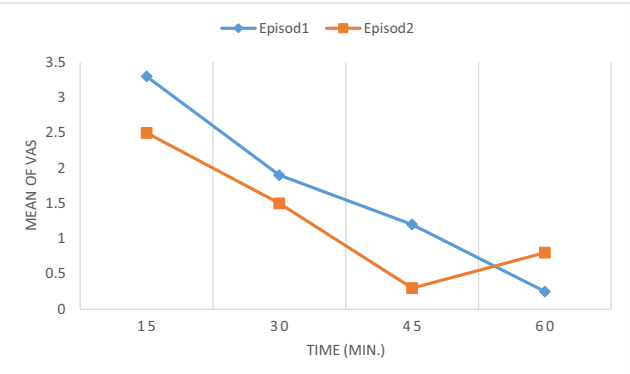

Fig. 2 p-values based on Mann-Whitney (in the times, before,p=0.0001,15 min p= 0.0001, 30 min p= 0.0001, 45 min p= 0.111, 60 min p= 0.117), The comparison of pain improvement in the two episodes (E1=1th episode,E2= 2th episode) of drug titration phase at different times

The mean frequency of pain episodes in the sublingual fentanyl group was 0.3±0.2 and it was 5.2±0.1 in the placebo group, which demonstrated a statistically significant difference (P=0.0001).

Comparing the pain intensity at different episodes in the two groups is shown in Fig. 6, which indicates statistically significant differences between the two groups at different times (P<0.001).

At this stage of the study, only 6 patients (12%) in the sublingual fentanyl group reported drowsiness.

Discussion

BTP is an important clinical challenge in taking care of patients with cancer. A drug formulation with a rapid onset can be effective. Thus, physicians are increasingly interested in developing drugs with this specificity to treat pain episodes.

The sublingual formulation, sublingual fentanyl, has a rapid onset of fentanyl and rapid onset of analgesia in the treatment of pain episodes.

In the present study, the primary effect of sublingual fentanyl 30 min after the drug administration compared with placebo and findings showed a significant decrease in episodic pain severity. Furthermore, the secondary effect of sublingual fentanyl 60 min after the drug administration compared to placebo showed a significant decrease. Taking sublingual fentanyl was preferred over placebo at all the studied time points [3, 12, 26] 60 min after the drug administration. This finding is consistent with the results of other studies [24, 42, 43].

In the current study, 15 min after taking sublingual fentanyl, the pain episode decreased significantly, indicating the efficacy of sublingual fentanyl with a rapid onset of analgesia in the treatment of pain episodes.

Additionally, in the titration phase of the drug, it was shown that sublingual fentanyl significantly relieved the intensity of episodic pain at doses of 100 μg and 200 μg. The side effects were also acceptable at these doses. This finding is in line with the results obtained from other studies [43–45].

In the drug titration phase, 100 patients (100%) successfully completed the titration phase. The success of the treatment in the titration phase is consistent with other studies carried out on oral transmucosal fentanyl [42, 43]. In another study, the treatment success in sublingual fentanyl titration was reported to be 59.5% in the treatment of pain episodes [24]. In another study, the success rate was 65% [42]. This is while it was 100% in this study. Effective titration doses of the drug were successfully determined in episodic pain control and effective analgesia with the lowest risk of drug-related adverse side effects [8].

Table 1 Demographic data of the two groups

	sublingual fentanyl group (n=50)	placebo group (*n*=50)	*P* value
Age (yr)	45.3±13.2	48.7±13.3	0.102
BMI (kg/m^2)	25.8±3.6	25.4±3.8	0.540
Sex;			
Male	25 (50.0%)	35 (70.0%)	0.041
Female	25 (50.0%)	15 (30.0%)	
type of cancer:			
colorectal	18 (36.0%)	21 (42.0%)	0.289
breast	15 (30.0%)	7 (14.0%)	
head & neck	9 (18.0%)	6 (12.0%)	
bone	2 (4.0%)	5 (10.0%)	
skin	1 (2.0%)	2 (4.0%)	
ovary	3 (6.0%)	3 (6.0%)	
stomach	2 (4.0%)	6 (12.0%)	
type of cancer pain:			
nosceptive	32 (64.0%)	30 (60.0%)	0.058
neuropathy	4 (8.0%)	12 (24.0%)	
mixed	14 (28.0%)	8 (16.0%)	

In general, the drug was well-tolerated by all the patients in the drug titration phase and all the patients entered the double-blind phase from the drug titration phase. This finding is in line with the results of other studies [24].

In the titration phase of this study, the most common drug-related side effects were drowsiness (20 patients), dizziness (7 patients), and nausea (4 patients), commonly seen in opioid analgesics [44, 45]. In the long-term double-blind phase, only 6 patients experienced drowsiness. According to the findings of the present study, the long-term use of sublingual fentanyl has a good safety profile.

In the double-blind phase of the current study, at different episodes and at different time points (15,30,45,60 min) after the drug administration, taking the sublingual fentanyl significantly improved the episode pain intensity.

Previous studies have shown the rapid opioid sublingual formulation of fentanyl with a pharmacokinetic profile of the drug, which is closely consistent with the time profile of the

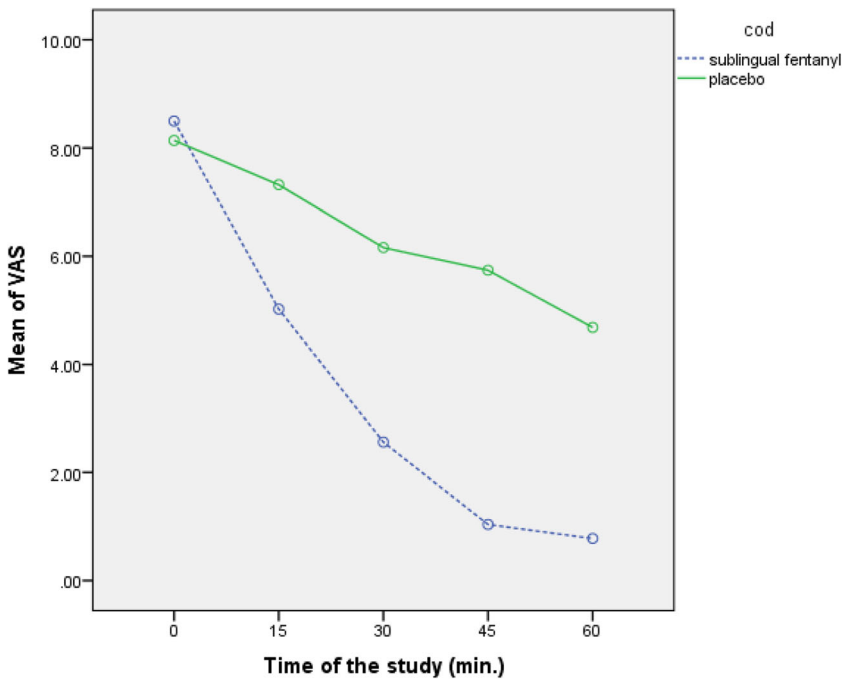

Fig. 3 *p*-values based on repeated measurement ANOVA,The comparison of pain relief changes in the first episode between the sublingual fentanyl and placebo groups

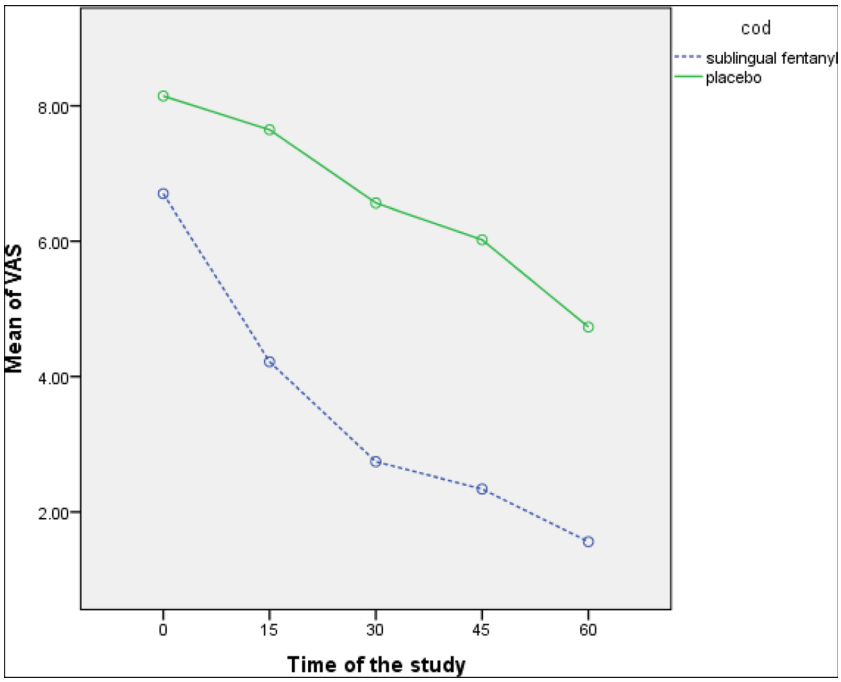

Fig. 4 *p*-values based on repeated measurement ANOVA, The comparison of pain relief changes in the second episode between the sublingual fentanyl and placebo groups

pain episode [37, 44], and its quick-acting feature improves the severity of the episode.

Sublingual fentanyl had a significant effect on episodic pain relief and indicated patients' good tolerance compared to placebo. Sublingual fentanyl provides significant analgesia in less than 15 min after the drug is administered to relieve episodic pain severity. Sublingual fentanyl is also safe and well-tolerated. The results obtained in our study with previous studies that reduce the severity of pain episode in cancer patients with other oral transmucosal fentanyl therapies, it was consistent [42, 43].

The results of our study confirm the results of the Phase I and II studies [22] showing rapid Sublingual fentanyl absorption and rapid-onset pain relief in opioid-tolerant patients with cancer suffering from the BTP.

The patients evaluated in this study included two sexes with a wide age range and different groups of underlying diseases. Our study population represented cancer patients

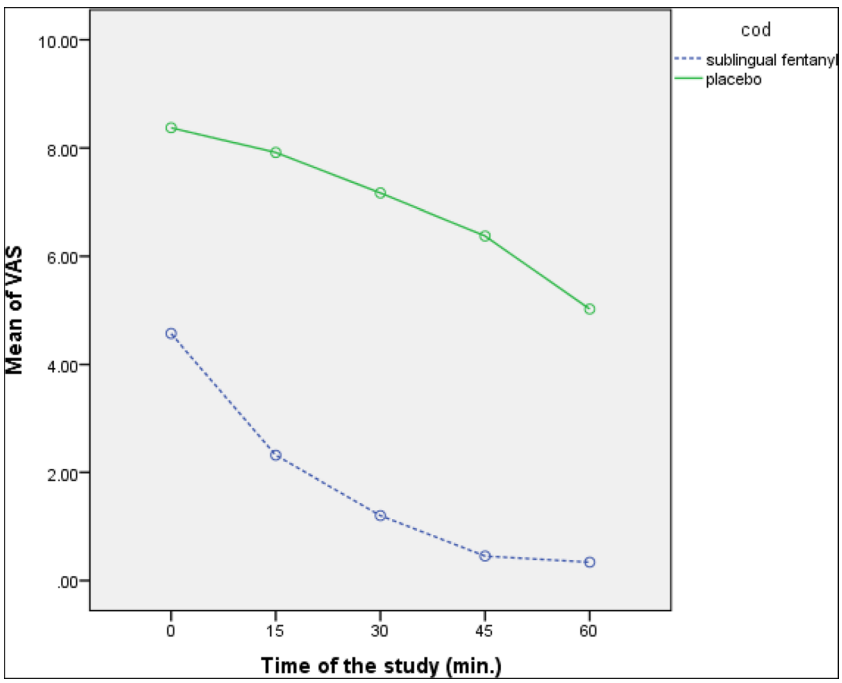

Fig. 5 *p*-values based on repeated measurement ANOVA,The comparison of pain relief changes 12 h after the first episode between the sublingual fentanyl and placebo groups

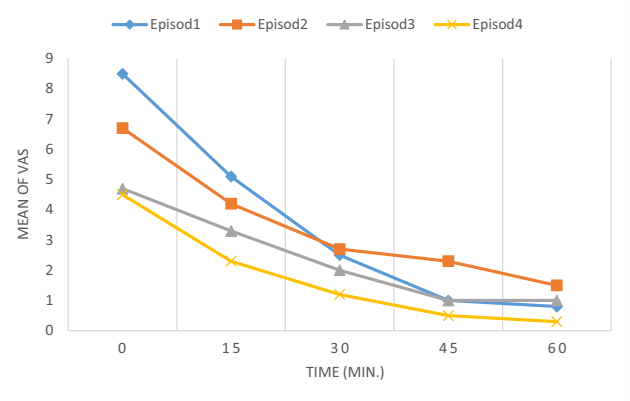

Fig. 6 *p*-values based on oneway-ANOVA. The comparison of pain relief at different episodes in the sublingual fentanyl group

who frequently presented to medical centers with a complaint of a sudden episode of pain. According to the results obtained in our study, the efficacy profiles and Sublingual fentanyl tolerance may have a significant impact on improving the living conditions of these patients. However, the effect of this drug on the patient's real-life environment is still under evaluation.

According to the findings of this study, sublingual fentanyl produced rapid analgesia, had a short-acting duration and was effective, safe, and well-tolerated by avoiding high sedation and minimal drug-related side effects even at a dose of 200 μg. This safe, simple, and easy method is a good choice in treating cancer-related pain episodes.

The limitations of the study included subjective expression of pain severity and pain relief and tools used to evaluate study endpoints, which significantly affects the evaluation of the effectiveness of therapeutic interventions and is known as response change. This aspect has not been addressed in our study, which has been shown to increase the risk of type 2 error [22, 44].

In the current study, the analgesic effect of the drug was not correlated with demographic information or previous opioid regimens. This study was conducted on a wide age range of men and women.

According to the results obtained in our study, to increase the duration of analgesia and reduce the number of pain episodes, sublingual fentanyl can be suggested to pain fellowships according to the protocol of the present study.

More research is needed on the efficacy, safety and tolerance profiles of sublingual fentanyl in these patients. It is recommended that further studies be performed with a larger sample size and longer follow-up time in terms of drug side effects, pain relief (BTP), quality of life and drug safety, taking into account the type and stage of cancer and the opioid regimen for chronic cancer-related pain to the management of cancer BTP with sublingual fentanyl tablet.

Conclusion

Sublingual fentanyl appears to be effective for patients with rapid-onset analgesia, has short-acting duration, is effective medication, safe, and well tolerated. It is a suitable choice in patients suffering from episodes of cancer-related pain.

Pain fellowships are advised to prescribe sublingual fentanyl tablets for the treatment of cancer-related pain episodes in patients following the protocol of the current study.

Compliance with ethical standards

Conflict of interest The authors claim no conflict of interest.

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