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ORIGINAL RESEARCH

Efficacy of Sublingual Fentanyl vs. Oral Morphine for Cancer-Related Breakthrough Pain

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ABSTRACT

Introduction: Breakthrough cancer pain (BTcP) is recognized as a clinically significant complication of chronic cancer pain with most BTcP episodes peaking in intensity within a few minutes and lasting for approximately 30 min. Although a number of rapid-onset fentanyl preparations have been developed in the last decade, BTcP is still typically managed through the use of rescue doses of oral morphine but a comparative study of sublingual fentanyl and oral morphine is still lacking. The aim of this study was to determine the efficacy, tolerability, and patient satisfaction of sublingual fentanyl citrate (SLF) and oral morphine solution (OM) in the treatment of BTcP.

Methods: In this prospective, longitudinal, controlled-study, 40 patients with BTcP were allocated to receive oral morphine (OM) or sublingual fentanyl (SLF). Pain intensity level on a 0–10 numerical rating visual analog scale (VAS), frequency of BTcP throughout the day, onset of relief (0–5, 6–10, 11–15, or over 16 min), time required for dose titration, patient satisfaction and adverse effects were assessed at 3, 7, 15, and 30 days after starting the treatment.

Results: Mean doses of opioids for BTcP were 235 ± 23.4 μg (SLF) and 38 ± 5.2 mg (OM). The mean pain intensity levels were significantly lower with SLF than OM at 3 days (6.0 vs. 6.95; $p = 0{,}001$), 7 days (4.15 vs. 6.25, $p < 0.001$), 15 days (3.45 vs. 5.35, $p < 0.001$), and 30 days (3.05 vs. 4.45, $p < 0.001$). SLF provided significantly faster relief for BTcP than OM ($p < 0.001$) with a shorter dose titration period (mean 6.6 ± 3.3 vs. 13.3 ± 4.9 days; $p < 0.001$) and better satisfaction scores and with a very good safety profile.

Conclusions: Administration of SLF might provide a more effective treatment option than oral morphine for BTcP.

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INTRODUCTION

Over 40% of patients with cancer suffer pain during the course of their disease and over 80% suffer moderate or severe pain in the advanced phases [1, 2]. In the majority of cases, the pain is chronic and caused by the tumor, but 50–90% of patients reported to experience intermittent flares of their pain [3–9], with an incidence rate that varies greatly depending on the stage of the disease (early stages 30–40%, late stages 70–90%) [10].

The term breakthrough pain (BTP) was first used in 1990 by Portenoy and Fine, who defined it as "a transitory exacerbation in pain intensity on a baseline pain of moderate intensity in patients on analgesic treatment regularly administered" [11, 12] and classified it into three types: incident pain, idiopathic pain, and end-of dose failure pain. Later, in 1998, Coluzzi [13] called this type of pain "episodic", dividing it into incident pain, crescendo pain, and end-of-dose failure pain but in the latest reviews, pain due to end-of-dose failure has been removed from the classifications of breakthrough pain. Finally, in 2004, Portenoy [4] stated certain common characteristics that define BTcP: severe in intensity [visual analog scale (VAS) >7], sudden in onset and short in duration (mean of 30 min).

Data from surveys suggest that BTcP is far from optimally treated [14–16] resulting in an increased perception of pain severity [17], decreased patient's quality of life [16], and a significant economic burden [18, 19]. BTcP is usually managed by rescue doses of oral morphine (OM) [20] but a major limitation of this approach is that the onset of action of this drug may not match the temporal characteristics of many BTcP episodes [21, 22]. Interest in rapid-onset opioids (ROO) to relieve BTcP has therefore been growing and new pharmaceutical forms for administration via oral mucosa with a shorter onset of action, such as sublingual fentanyl citrate orally disintegrating tablet (SLF), have been developed to provide us with new means for treating these episodes [23, 24]. SLF has proven to be effective in some placebo-controlled studies [24–27] but no direct comparisons regarding the relative contribution from pain relief between OM and SLF have been published.

The aim of this study was to determine the efficacy, tolerability, and patient satisfaction of sublingual fentanyl citrate (SLF) and oral morphine solution (OM) in the treatment of BTcP.

METHOD

Trial Design

This was a prospective, double-blind, controlled-study in which patients suffering from BTcP were consequently recruited and allocated (1:1) to receive oral morphine (OM) or sublingual fentanyl (SLF). Outcome assessors were kept blinded to the allocation. Physicians responsible for evaluating the results were unaware of how the patients were organized and therefore also of the treatments they were receiving.

Participants

Eligible participants were all adults aged 18 or over suffering from cancer pain whose background pain was treated with strong

opioids and who had BTcP which met the criteria described by Portenoy [11] (stable analgesia in the previous 48 h, controlled background pain in the previous 24 h, transient exacerbation of pain in the previous 24 h). The term strong opioid refers to medicines classified as being on step three of the World Health Organization (WHO) analgesic ladder. In Spain the strong opioids available include fentanyl, morphine, buprenorphine, oxycodone and tapentadol. Exclusion criteria were <18 years old, non-controlled basal pain, hospitalized, or cognitive disturbances.

Study Settings

The study took place at the Oncology Unit of the Hospital de Alta Resolución in Guadix, Granada, and the Hospital Comarcal in Melilla from January 2011 to January 2013.

Intervention

Patients were assigned to receive sublingual fentanyl tablet (SLF; ABSTRAL® ProStrakan Farmacéutica, S.L.U., Madrid, Spain) or oral morphine solution (OM). Doses, in both groups of treatment (MOR and FSL) were adjusted individually, regardless of the basal opioid dose used, and the dose was adjusted until an effective dose was obtained. The "effective dose" was defined as the dose needed to control the BTP (pain reduction by 50% in each pain episode without the occurrence of relevant adverse events).

Allocation was performed consecutively and alternately, with the Fentanyl group initiating the first sequence of dose allocation. The physician responsible for patient recruitment for each group was not involved in the data collection process. Therefore, he/she was unaware of which drug had been administered to the patients. Physicians who performed the follow-up visits were kept blinded as to the drug used in the treatment of BTcP. This was done by always using the term "rescue" when referring to the requests for BTcP medication.

To determine the sample size, the research support team at the Guadalix hospital was consulted and they determined that a total population of 40 patients was enough to be able to obtain reliable results with statistically significant differences.

Outcomes

The primary results with regards to efficacy in BTcP management were pain intensity reduction on a 0–10 numerical rating on the visual analog scale (VAS), frequency of BTcP throughout the day, and onset of relief (0–5, 6–10, 11–15, or over 16 min). This was carried out by providing patients with a pain diary which reflected the number of episodes, times of medication intake, and the time elapsed until pain relief was noted. Secondary outcomes included the assessment of the time required for dose titration, patient satisfaction, and identification of undesirable effects that may be associated with the use of both drugs in patients with BTcP. The side effects were assessed by a physician at each visit using a closed questionnaire. After the closed questionnaire, patients were then asked if they had noted anything more than what was mentioned in the interview. Satisfaction rates with the analgesic treatment were classified as: very satisfied, satisfied, dissatisfied, and very dissatisfied.

All outcomes were assessed at 3, 7, 15, and 30 days after starting the treatment. The first two assessments were performed by telephone and the last two in person.

Statistical Analysis

Statistical analysis included an intention to treat (ITT) approach that included all patients in the population who treated at least one BTcP pain episode with SLF or OM. The safety analysis set included all patients who received al least one dose of these drugs. For qualitative variables, absolute and relative frequencies were obtained and are expressed in percentages. The mean values of the episodes treated with both drugs were assessed for each time period. The differences in quantitative variables were measured per group using the Mann–Whitney *U* test, considering *p* values below 0.05 as significant. The SPSS Statistics V.17 for Windows (SPSS Inc., Chicago, USA) was used.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

RESULTS

Characteristics of the Sample at Baseline

A total of 40 patients consented to participate and were randomly assigned to one of the two study groups. Baseline demographics and clinical characteristics of each group are described in Table 1. Mean age was 65.90 ± 8.53 (OM) and 65.25 ± 8.45 (SLF) and most of the subjects were male (56.7% in the OM group and 57.4% in the SLF group). The most prevalent cancer types in descending

Table 1 Baseline demographic and clinical characteristics

	OM solution (*N* = 20)	**Fentanyl SL (*N* = 20)**
Age (years)	65.90 (8.53)	65.25 (8.45)
Sex (female)	1,280 (43.3%)	1,267 (42.6%)
Cancer type	6 prostate cancer	4 prostate cancer
	4 lung cancer	2 lung cancer
	2 breast cancer	4 breast cancer
	2 uterine cancer	3 uterine cancer
	2 pancreatic cancer	2 pancreatic cancer
	2 colorectal cancer	3 colorectal cancer
	1 ovarian cancer	1 ovarian cancer
	1 gastric cancer	1 multiple myeloma
Background opioid	4 Fentanyl TTS (3: 75 μg/h; 1: 50 μg/h)	7 Fentanyl TTS (2: 100 μg/h; 5: 50 μg/h)
	7 Oxycodone–naloxone (2: 80 mg/day; 5: 40 mg/day)	6 Oxycodone–naloxone (1: 80 mg/day; 5: 40 mg/day)
	4 Hydromorphone (2: 32 mg/day; 2: 16 mg/day)	5 Hydromorphone (1: 32 mg/day; 4: 16 mg/day)
	5 Tapentadol (1: 500 mg/day; 4: 300 mg/day)	2 Tapentadol (1: 500 mg/day; 1: 300 mg/day)

Data are means (SD), numbers or percentages (%). No significant difference between groups
OM oral morphine, *SL* sublingual

order for both treatment groups were prostate, lung, and breast cancer.

Background opioid treatment was: fentanyl transdermal (TTS) ($n = 11$: 2 patients 100 μg/h; 3 patients 75 μg/h; 6 patients 50 μg/h); oxycodone–naloxone ($n = 13$: 3 patients 80 mg/day; 10 patients 40 mg/day); hydromorphone ($n = 9$: 3 patients 32 mg/day; 6 patients 16 mg/day); tapentadol ($n = 7$: 2 patients 500 mg/day; 4 patients 400 mg/day; 1, 300 mg/day).

Pain Intensity Level, Onset of Relief, and Dose Titration Period

Incident pain was the more frequent type of BTcP in both groups of patients (Table 2). Mean doses of opioids were 235 ± 23.4 μg (SLF) and 38 ± 5.2 mg (OM).

The mean pain intensity level was consistently better for SLF than OM at all recorded time points (Fig. 1) with a significance of $p = 0.001$ at day 3, and greater ($p < 0.001$) at the other recorded time periods. A significant statistical difference between mean pain intensity level at baseline and at 30 days after starting the treatment was obtained in both treatment groups ($p < 0.001$). Onset of relief at day 3 compared to that of day 30 was significantly reduced in patients treated with SLF ($p = 0.001$) as compared to patients treated with OM ($p = 0.003$).

Sublingual fentanyl citrate provided faster onset of relief ($p < 0.001$) in BTcP (Fig. 2) and

Table 2 BTcP type, mean opioid dose and dose adjustment in patients treated with oral morphine solution and sublingual fentanyl

	Oral morphine solution ($N = 20$)	**Fentanyl SL ($N = 20$)**
BTcP type	Incident 14 (70%)	Incident 12 (60%)
	Idiopathic 6 (30%)	Idiopathic 8 (40%)
Mean opioid dose	38 ± 5.2 mg	235 ± 23.4 μg
Dose titration	13.3 ± 4.9 days	6.6 ± 3.3 days

Data are means (SD) or numbers (%)

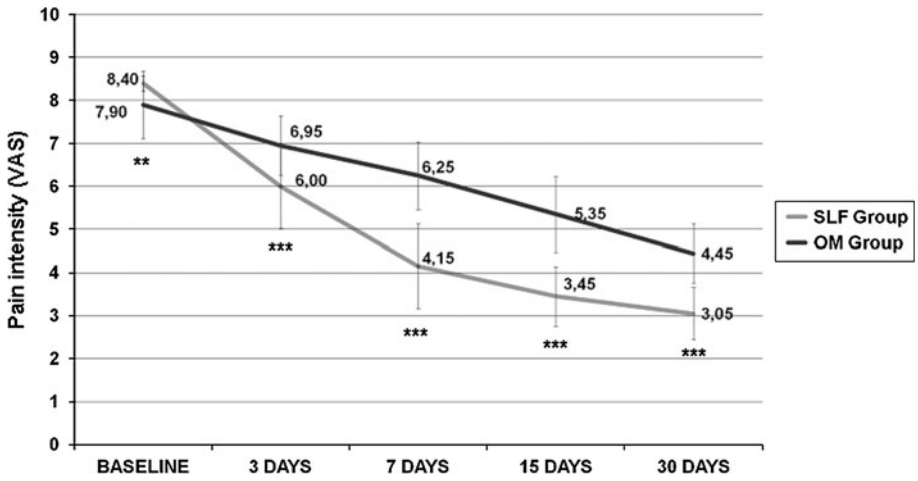

Fig. 1 Mean pain intensity (assessed by a numeric 1–10 visual analog scale) at baseline and at 3, 7, 15, 30 days after starting treatment with sublingual fentanyl (SLF) or oral morphine solution (OM). $^{**}p = 0.001$; $^{***}p < 0.001$

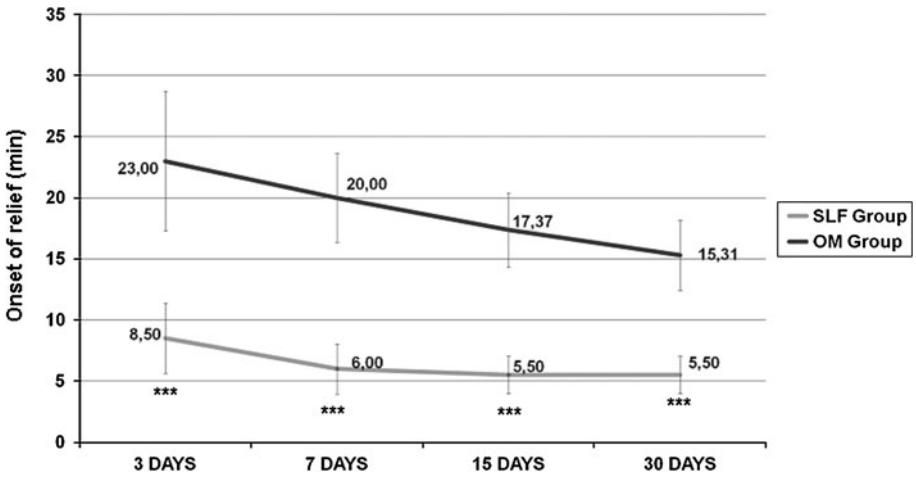

Fig. 2 Onset of relief (minutes) at baseline and at 3, 7, 15, 30 days after starting treatment with sublingual fentanyl (SLF) or oral morphine solution (OM). $^{***}p < 0.001$

improved pain scores with a shorter dose titration period (mean 6.6 ± 3.3 vs. 13.3 ± 4.9; $p < 0.001$) (Table 2).

Patient Satisfaction

In the group treated with SLF no patient reported dissatisfaction with treatment for BTcP, but 37.5% of the patients treated with OM reported being dissatisfied (31.25%) or very dissatisfied (6.25%). A great percentage of patients treated with SLF were very satisfied (65%) with the treatment, but in the group treated with OM the percentage was reduced to 12.5% (Table 3).

Side Effects

Side effects were similar with both treatments and typical of opioid drugs (Table 3). Vomiting was more frequent in patients treated with OM and somnolence for those patients treated with SLF. One patient discontinued treatment with OM due to the side effects and two patients discontinued OM intake due to the lack of efficacy.

Table 3 Satisfaction rates and side effects in patients treated with oral morphine solution and sublingual fentanyl

	Oral morphine solution ($N = 20$)	**Fentanyl SL ($N = 20$)**
Satisfaction	Very satisfied: 10%	Very satisfied: 65%
	Satisfied: 55%	Satisfied: 35%
	Dissatisfied: 25%	
	Very dissatisfied: 5%	
	Withdrawals: 1	
Undesirable effects	Constipation 3 (15%)	Constipation 3 (15%)
	Vomiting 3 (15%)	Vomiting 1 (5%)
	Nausea 3 (15%)	Nausea 3 (15%)
	Somnolence 1 (5%)	Somnolence 2 (10%)

DISCUSSION

Rapid-onset opioids, such as SLF, have gained growing popularity for the treatment of BTcP in recent years due to their rapid effect and their non-invasive form, but comparison studies with

the traditionally used OM were still lacking. This is the first prospective study carried out to directly compare the efficacy of OM and SLF in patients suffering from BTcP. As was hypothesized, SLF provided remarkable pain relief as compared to OM throughout the period of study.

Sublingual fentanyl citrate is a new pharmaceutical form which uses the conditions in the sublingual environment to obtain a rapid absorption of fentanyl, which in turn results in a rapid onset of the analgesic action. At 1 min, 75% of the active substance has dissolved and at 3 min over 95%, in only 0.025 ml of saliva [28]. Sublingual administration of opioids provides a non-invasive mechanism for faster absorption and a more effective onset of pain relief. As it is highly lipophilic, fentanyl easily crosses the blood–brain barrier and absorption through the buccal mucosa is gradual and predictable [29]. This system thereby achieves optimal exposure of the active substance, in quantity and time and the drug can be detected in plasma in 8–11 min, with low inter-individual variability and linear pharmacokinetics at the doses studied and an estimated onset of action of 5–15 min [27]. In contrast, analgesic onset of oral morphine has been estimated at 30–45 min [30]. Therefore, SLF has a better pharmacological profile more suited to the characteristics of BTcP (i.e., rapid onset of effects and relatively fast acting) than the slower acting opioid OM, providing faster relief in BTcP attacks with a shorter dose titration period and a very good safety profile.

Some previous studies assessed the efficacy of SLF compared to placebo in BTcP [23–26] and their findings are in accordance to our results. Lennernäs et al. evaluated the efficacy and tolerability of SLF in a sample of patients who were randomized to receive single doses of 100, 200, or 400 μg of SLF, or placebo. 400 μg SLF was significantly more effective in reducing pain intensity and requirements for rescue analgesia than placebo, but 100 and 200 μg SLF doses compared with placebo did not reach significance at any point. Adverse effects were mild to moderate and the incidence did not increase with increasing SLF dose [23]. In the study of Rauck et al. [24], SLF provided significant improvements in pain relief and pain intensity scores from 10 min post-dose relative to placebo with an acceptable safety profile confirmed in long-term follow-up (over 12 months of treatment). More recently, a meta-analysis incorporating this study performed an indirect comparison between OM and SLF and revealed that although SLF provide superior pain relief than placebo in the first 30 min after dosing (66% probability of superior pain relief), oral morphine performed little better than placebo (56% probability) [31].

In 2011, the American Pain Foundation published one report that described the opinions and problems of BTcP treatment from the patient perspective. Important findings were that: 58% of the patients claimed the analgesic efficacy of breakthrough pain treatment to be inadequate and 50% of patients considered that physicians did not view quality of life as an important aspect of treatment [32]. Improvement in patients' quality of life with SLF were reported by Überall and Müller-Schwefe [25] in a prospective, multi-center phase IV study carried out in opioid-tolerant adult patients with BTcP. In a separate phase III study evaluating long-term effectiveness of SLF, patients reported high levels of satisfaction with the formulation and the levels of satisfaction did not diminish with prolonged treatment [26] which suggests an adequate balance between efficacy and tolerability. Our findings suggest that together with the high degree of effectiveness, SLF

formulation has provided a good tolerability and optimal satisfaction rates, far better than those shown by OM. Indirect evidence from patient preference surveys [33] which take into account the mode of administration and efficacy as well as tolerability, indicate that the fentanyl preparations might have some advantages over oral morphine beyond efficacy and it could potentially be argued that the prolonged duration of action of OM in comparison with the fentanyl preparations might result in an extended opportunity for adverse events [34].

In BTcP, opioids should be individually titrated to an effective dose that provides adequate analgesia and minimizes undesirable effects. To reach the safest effective dose for the individual patient as soon as possible, the dose titration process is critical. The shorter time required for dose titration observed with SLF compared to OM together with its faster onset of action represents important advantages in BTcP control. Finally, the choice of the dose of ROO to be prescribed remains controversial [35] and some authors have proposed establishment of doses that are proportional to basal opioid regimens for background pain because this seems to be effective and safe in the majority of patients [36, 37].

The SLF was approved in the EU in 2008 and in the US in 2011 (both under the brand name ABSTRAL) for BTcP in opioid-tolerant adults with cancer. Since then it has proven efficacy in reducing BTcP in patients with cancer who are opioid tolerant and multitude of patients have been exposed to this dosage form. Factors that should be considered when selecting the most appropriate formulation include individual patient characteristics, likelihood of adherence, characteristics of their BTcP, cost and formulation preferences. Patient attributes that may be relevant include a lack of physical dexterity or weakness; this may make administration of oral formulations more difficult because it requires active patient participation. Mucositis, which is a common problem in patients with cancer, may also influence the choice of an appropriate formulation, although studies with SLF have shown that these interventions are well tolerated in patients with mucositis [38].There are surprisingly few data on patient preferences for BTcP interventions. An evaluation of the acceptability of different routes of analgesia for BTcP in patients with cancer-related BTcP demonstrated that 63%, of patients reported that they would find it acceptable to take sublingual medication for mild/moderate BTcP and for severe BTcP the rates were 75% [39]. SLF shows some advantages such as rapid onset of action and can be used by patients who are unable to swallow or find medications difficult to swallow due to nausea/vomiting. There is a lack of pharmacoeconomic studies assessing the net benefit of SLF to oral opioids to assist decision-making by patients, clinicians, and payers but the administration ROO for the treatment of BTcP has demonstrated to be cost-effective [40].

The principal limitations of this study were the non-randomization of the sample, the specific setting of two units with specific features and the relatively low number of patients. No power calculation was performed so the possibility of a type II error should be considered. This observation should be followed-up by further randomized studies with a larger number of patients and different settings.

CONCLUSIONS

The aim of this study was to determine the efficacy, tolerability, and patient satisfaction of sublingual SLF and OM in the treatment of BTcP and we can conclude that the SLF provides

adequate pharmacological tools to the armamentarium of BTcP with clinical significance by a high effectiveness, good tolerability, and improved quality of life in these patients. Administration of SLF might provide a more effective treatment option than OM for BTcP.

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Conflict of interest. Ignacio Velázquez Rivera, José Carlos Muñoz Garrido, Pilar García Velasco, Inmaculada España Ximénez de Enciso and Lourdes Velázquez Clavarana declare that they have no conflict of interest.

Compliance with ethics guidelines. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

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