Fentanyl buccal tablet versus oral oxycodone for Emergency Department treatment of musculoskeletal pain

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ABSTRACT

Background: Emergency Department (ED) analgesia can potentially be delivered quickly using transbuccal administration. A previous study identified time-of-onset advantage of a 100 mcg fentanyl buccal tablet (FBT) as compared to a dose of 5 mg oxycodone with 325 mg acetaminophen. The current study reports comparison of higher-dose (200 mcg) FBT as compared to a more commonly used oxycodone dose of 10 mg with 650 mg acetaminophen.

Methods: Time frame: Patients were enrolled between October 2012 and October 2014.

Setting: The study was conducted in an urban teaching ED with annual census of 55,000.

Patients: The 50 convenience-sampled cases met eligibility criteria of age 18-60, with isolated orthopedic complaints; subjects required X-ray to rule-out fracture, and to have pain sufficient to warrant opioids.

Interventions: In this double-blind placebo-controlled analgesia trial, patients were randomized to one of two study groups. OXY subjects received two orally ingested tablets, each containing 5 mg oxycodone and 325 mg acetaminophen, and a transbuccal inactive comparator. FBT subjects received two placebo oral tablets and a 200 mcg FBT.

Data: The main study endpoint was achievement of at least two points' reduction in numeric pain rating scale (NPRS) within ten minutes of study drug administration. NPRS was assessed at the time of study entry and every five minutes post-drug administration for an hour. Secondary endpoints included assessment of side effects and subjects' desire to have the same medication for future similar pain.

Analysis: Categorical data were assessed with binomial exact 95% confidence intervals (CIs). Continuous data, after being demonstrated as non-normal with skewness-kurtosis testing, were analyzed with Kruskal-Wallis testing. Multivariate Cox proportional hazards analysis was performed to assess whether, after adjustment for potential confounders, there was a difference between FBT and OXY groups with respect to time to achieving significant analgesia.

Results: Study groups were similar with respect to age (medians: OXY 34, FBT 38, p = 0.47), initial pain score (median 8 in each group), sex (proportion of males: OXY 64%, FBT 48%, p = 0.25), and ethnicity (proportion of whites: OXY 68%, FBT 56%, p = 0.38). The same proportion (52%) of OXY and FBT cases achieved significant reduction in pain within 15 minutes. Multivariate Cox regression adjusting for potential confounders confirmed (p = 0.28) no difference in rates of pain reduction between OXY and FBT. There were no major complications in either group. The majority of subjects in each group (80% in FBT group versus 76% in OXY group, p = 0.73) expressed high satisfaction and preference to receive the same regimen in future.

Conclusion: This study’s results suggest approximate equivalence between 200 mcg FBT and 10 mg oxycodone with 650 mg acetaminophen, with respect to time-to-analgesia, analgesic efficacy, side effects, and patient satisfaction.

Keywords: analgesia, transbuccal, fentanyl, oxycodone, emergency department
BACKGROUND
Provision of timely and adequate analgesia is an important goal in the Emergency Department (ED). In the often busy acute care setting, however, relief of patients’ pain can be suboptimal in terms of both timing and efficacy. The problem, denoted ED “oligoanalgesia” decades ago, has been addressed over the years but there is still room for improvement. 1

For patients at the non-critical end of the acuity spectrum, barriers to rapid analgesia include the lack of a registered nurse (RN) and related resources required for quickly administering analgesia by the parenteral route. Some patients who are in significant pain lack intravenous (IV) access, and delays in placing vascular lines are a well-known reason for analgesia delay. 4 Although more-rapid IV placement may be part of the solution for improved pain care, there remains a role for alternative means to rapidly provide pain relief.

One method of quickly delivering analgesia is the transbuccal tablet. 3 Used for rapid relief of breakthrough cancer pain, transbuccal tablets have been important in the outpatient setting. 5 Potent opioid delivery via the transbuccal route has been preliminarily assessed for use in acute care, in a pilot study assessing safety and efficacy of fentanyl buccal tablet (FBT) analgesia in the ED. 6 Since it was the first such ED study of a formulation initially intended (and labeled) for opioid-tolerant cancer patients, a conservative approach dictated that the initial study employ a relatively low dose (100 mcg) of FBT. 6

As compared against a similarly low dose of “standard opioid therapy” (5 mg oxycodone, 325 mg acetaminophen), the 100 mcg FBT showed promise. 6 No side effects or concerns were identified in the initial study, and FBT subjects had a faster time to achievement of significant pain relief. That initial study concluded there was reasonable basis for further investigation of FBT in a higher dose that was more comparable to the usual ED dose of 10 mg oxycodone.

Based upon the results of the initial study, the current follow-up study was executed as a randomized, double-blinded, controlled, convenience-sample clinical trial. The primary goal was to assess whether the advantages of FBT over oral-tablet oxycodone that were suggested at lower doses, were present when usual doses were used. Secondary goals included assessment of side effects, and also assessment as to whether patients preferred one regimen (FBT or oral oxycodone) over another.

METHODS
Design and setting
The study was a prospective, randomized controlled trial. Subjects were enrolled as a convenience sample (based upon research assistant availability) between 2012 and 2014. The study center was the Fast Track i.e. non-critical patient area in an urban academic ED with annual census of approximately 55,000. The ED cases comprising the study population were seen by Emergency Medicine (EM) residents with EM attending supervision.

Ethics review and regulatory oversight
The hospital and university institutional review (ethics) boards approved the study. The protocol was also approved by the U.S. Food and Drug Administration (FDA) under Investigational New Drug (IND) regulations (FDA IND# 77096, www.fda.gov).

Study subjects
Patients who were eligible for the study were those between ages 18–60, with isolated orthopedic injuries that were judged sufficiently significant to require X-ray imaging. Patients were eligible for the study if they decided their pain was of sufficient severity to warrant analgesia stronger than acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen.

To be entered into the study, patients had to have no hemodynamic or other instability and had to be judged by the physician to have simple musculoskeletal injury with no complicating factors. Patients with history of chronic opioid use or abuse, or those judged by the treating physician as having opioid contraindications, were ineligible for the study.

Other exclusion criteria included allergy to any of the study drugs, breastfeeding, concurrent therapy with medications (phenothiazines, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors) or ingestants (e.g. alcohol, benzodiazepines) that could interact with opioids. Any patient who had previously taken lansoprazole buccal tablets was excluded from study participation due to
potential for unblinding; see below. Patients were excluded if they had already received pain medication, and female patients were required to have a negative pregnancy test before enrollment.

Interventions
As part of the study protocol's safety monitoring, patients had to agree to stay in the ED for at least an hour after study medication administration. The initial study protocol required two hours’ observation period but with FDA and IRB clearances the study protocol was modified to allow one-hour observation after the initial 20 subjects were entered and had no problems with vital signs. By study protocol, new vital signs abnormalities were defined to have developed if: SBP fell below 90; HR rose above 120 or fell below 60; RR dropped below 12; or SaO2 dropped below 95%. Study protocol called for more-frequent assessment if abnormal findings were noted; this was ultimately unnecessary.

Once eligible patients were identified, study staff discussed the trial with patients and obtained informed consent. Study subjects were randomly assigned to one of two groups: FBT or OXY.

OXY subjects received two orally ingested tablets, each containing 5 mg oxycodone and 325 mg acetaminophen (Percocet®, Endo Pharmaceuticals, Malvern PA). This preparation of oxycodone is a standard (i.e. not sustained- or delayed-release) oral medication used in the United States. OXY subjects also received an inactive (no analgesic effect) transbuccal comparator (lansoprazole 15 mg, Prevacid SoluTab®, Wyeth, Madison NJ). The inactive comparator was used in keeping with methodology of the first ED FBT. In short, there is a lack of ability to easily manufacture placebo transbuccal tablets, and the plan for use of the lansoprazole (which has no analgesic effect for musculoskeletal pain) was generated in conjunction with the FDA.

FTB subjects received two placebo oral tablets and a 200 mcg FTB tablet (Fentora®, Cephalon, Frazer PA). All medications were delivered from the research pharmacy in fully blinded “pairs” of transbuccal and oral tablet medication/placebo sets. The administration route that contained active analgesia was not known to patients, treating physicians/nurses, research assistants (i.e. data collectors), or study statisticians (i.e. data analysts).

Outcomes
Pain intensity was assessed using a standard 0–10 numeric pain rating scale (NPRS) commonly used in ED practice and acute-care pain studies. Pain intensity was assessed every five minutes for one hour. Study staff accompanied patients if they left the ED for radiographic studies, so as to prevent interruptions of gathering of pain level and vital signs data.

After 45 minutes, patients were eligible for rescue medication. Rescue medication was given at the discretion of the treating physician.

At the conclusion of the study hour, patients were asked to guess whether their oral pills or transbuccal tablet had contained the active analgesic medication. Patients were also asked to indicate, using a standard Likert scale (1 through 5 indicating strong disagreement through strong agreement), whether they would want the same medication they had just received in the event of future episodes of similar pain.

Data and analysis
The data collected included demographics (subject age, sex, and ethnicity) as well as NPRS and vital signs information. NPRS drop of at least two points (e.g. from 8 to 6) was defined as representing “significant pain relief.” The primary study endpoint was whether significant pain relief was obtained within 10 minutes of study drug administration. The 10 minute time frame was selected for the endpoint, based upon the median time to significant pain relief as identified in the earlier study of FBT use in the ED. Secondary endpoints included occurrence rates of side effects, and patients’ expressed preference for receiving the same medication for future episodes of pain.

Proportions data were reported with 95% binomial exact confidence intervals (CIs) and compared with chi-squared testing. After skewness-kurtosis testing revealed non-normal distributions, central tendencies for these data were reported with median and interquartile range (IQR). Between-group comparisons for continuous confounders were executed with nonparametric Kruskal-Wallis testing. Although groups’ overall characteristics were anticipated (and ultimately confirmed) to be similar due to randomization, the study analysis plan incorporated multivariate Cox proportional hazards analysis which was used to adjust for potential confounders while assessing time-to-analgesia.
(i.e. time to two-point NPRS reduction) for FBT and OXY groups. Analysis was performed with the Statistical Analysis System (SAS) (Cary, North Carolina); significance was defined at the p < 0.05 level.

RESULTS

Subjects

The 50 study subjects' demographics and diagnostic information are outlined in the Table 1. For all comparisons between FBT and OXY, there were no significant intergroup differences (p > 0.05 for all comparisons) in subjects' characteristics.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fentanyl group</th>
<th>Oxycodone group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>25</td>
<td>25</td>
<td>0.47</td>
</tr>
<tr>
<td>Age median</td>
<td>38 (IQR 28–49)</td>
<td>34 (IQR 26–43)</td>
<td></td>
</tr>
<tr>
<td>% Male</td>
<td>64%</td>
<td>48%</td>
<td>0.25</td>
</tr>
<tr>
<td>Baseline pain median</td>
<td>8 (IQR 7–9)</td>
<td>8 (IQR 8–10)</td>
<td>0.42</td>
</tr>
<tr>
<td>Race Black</td>
<td>10 (40%)</td>
<td>7 (28%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Other White</td>
<td>14 (56%)</td>
<td>17 (68%)</td>
<td></td>
</tr>
<tr>
<td>Other Other</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>% Fracture</td>
<td>9 (36%)</td>
<td>8 (32%)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

* IQR = Interquartile range

Blinding success

Study subject blinding was explicitly assessed, and was successful. Ten of the FBT subjects (40%), and 11 of the OXY subjects (44%), guessed they received active medication via the transbuccal route (p = 0.77).

Pain score reduction

There was no difference between FBT and OXY with respect to any of the pain relief endpoints. Significant pain reduction (at least two points' drop in NPRS) was achieved by most subjects in both groups (80% FBT, 88% OXY, p = 0.44, 95% CI for risk ratio, 0.7 to 2.4).

For the a priori endpoint of pain levels in 10 minutes, there was no difference (p = 0.84) between the FBT median (8, IQR 6–8) and the OXY median (7, IQR 5–9). Just over half (52%) of FBT subjects, and the same proportion of OXY subjects, had significant pain relief at 15 minutes post-study drug administration.

Multivariate Cox regression adjusting for age, race/ethnicity, initial pain score, and sex confirmed similar rates of pain reduction for OXY and FBT subjects (p = 0.28, proportional hazard regression 95% CI, 0.4 to 1.5).

Rescue medication

Three subjects in each group received rescue medication (ketorolac or opioid) at either the 45 or 60 minute time mark after study medication administration. An additional two patients in each group received rescue medication after the 1 hour time mark after study medication administration.

Side effects

There were no significant side effects in either group. No patient required unblinding or intervention other than with diphenhydramine; diphenhydramine was administered for uncomplicated pruritus in two patients in the FBT group and a single OXY patient (p = 0.55). Other than pruritus, during the two-hour observation period there were six FBT and five OXY patients (p = 0.73) who reported various symptoms (light-headedness, dry mouth, headache), none of which required intervention.

There were no new vital signs abnormalities or problems in the study subjects. There was no new tachycardia (HR > 100), bradycardia (HR < 60), hypertension (SBP > 140), hypotension (SBP < 90), or hypoxemia (S_O2 < 95%) in any patient.

The study protocol set out to assess nausea on an ordinal (0–10) scale, but the symptom was uncommon and its new (post-study medication) occurrence was not noted. Nausea was treated by...
clinicians as per their standard care (treatment did not require unblinding). At the time of randomization (i.e. prior to administration of study medication), four FBT cases and two OXY cases noted nausea. Nausea improved within an hour in all cases, and no new nausea developed in either study group.

**Subjects’ preference to receive same medication in future**

There was minimal difference \( p = 0.73 \) between proportions of FBT (80%) and OXY (76%) subjects expressing the opinion they’d want the same medication they received in the study, in case of future episodes of similar pain.

**DISCUSSION**

With increasing demands on EDs related to higher patient loads, the ability of EM practitioners to quickly and adequately treat pain is sometimes restricted. In particular, data indicate that there are notable problems with administration delays and suboptimal pain reduction for patients with “minor” musculoskeletal injuries (e.g. sprains and fractures).\(^ {11,12} \) While non-pharmacological measures such as splinting and immobilization are important means to reduce pain in such patients, there is also need for analgesia provision.

Of the available therapies in use for ED analgesia for musculoskeletal conditions, NSAIDs and opioids are among the more commonly utilized. Both of these classes of analgesics have been, and will continue to be, useful in many patients with musculoskeletal injuries. However, each is associated with disadvantages inherent to either the drug class or the current routes of administration.

NSAIDs incur well-characterized general risks (e.g. ulcers) and have also been associated with specific risks of bleeding and non-union when used for fracture analgesia.\(^ {13,14} \) Opioids are useful for pain relief via many administration routes, but these medications are optimally administered via the IV route.\(^ {4} \) Use of the IV route is associated with more-rapid analgesic onset, reduced drug absorption variability, and enhanced ability to titrate medication to pain relief, but establishment of vascular access requires time, RN resources, and a stretcher upon which the patient can be placed.

Non-opioid, non-NSAID approaches to acute-care analgesia have been reported over the years. Interventions ranging from inhaled gases to physical stimulation have been investigated and occasionally reported useful in a variety of settings.\(^ {15–18} \) However, for a variety of reasons, none of these approaches have been adopted in widespread fashion. There is thus reason to investigate whether a novel approach to delivery of rapidly effective analgesia can be identified for ED patients.

One of the initial directions for EM practitioners investigating means to provide rapid pain relief (without having to institute IV access), was to utilize non-standard delivery routes for analgesia. Fentanyl, administered by intranasal or orally absorbed forms (including lozenge and transbuccal tablet) delivery, has been used in a variety of settings for procedural sedation and analgesia.\(^ {3,19–23} \) Overall performance has been good, although there are still problems with tolerance (predominantly for intranasal delivery) and nausea (associated with lozenge forms of fentanyl).\(^ {19,24} \) Existing evidence supports continued exploration of the “ideal” method for delivering rapid analgesia with minimal risk and side effect profile.

Fentanyl administered via transbuccal tablet results in rapid drug delivery — with faster systemic uptake than fentanyl lozenges — but the FBT seems to incur less nausea than other oral delivery routes such as the lozenge.\(^ {6,25} \) The FBT has undergone limited evaluation in the ED setting, probably because of a “black-box warning” against its use in patients who are opioid-naïve.\(^ {6} \) For this reason, the initial evaluation of FBT use in the ED employed a dosage that would be considered conservative: 100 mcg FBT was compared with a single oral pill containing 5 mg oxycodone combined with 325 mg acetaminophen. That initial trial was promising, but the conclusions were necessarily limited given both patient numbers and the lower-than-usual dose of the oxycodone control.

As a follow-up to the initial FBT study, the current evaluation was undertaken to assess performance of FBT as compared to analgesic safety and efficacy provided by a more-usual dose of oxycodone (10 mg oxycodone with 650 mg acetaminophen). The FBT dose was doubled to 200 mcg, administered in a single transbuccal tablet; the comparison group received active medications in the form of two oxycodone tablets.

The current study identified no differences between FBT and OXY subjects with respect to degree of analgesia provision, timeline to pain relief, occurrence of side effects, or patient preference for same-drug analgesia in future. The most appropriate conclusion that can be drawn from this study’s data,
is that 200 mcg FBT should be considered a rough equivalent to a pair of oxycodone/acetaminophen 5/325 mg tablets.

While providing a guide to consideration of the potential place for FBT in the ED pharmacopoeia, the current study does have a number of limitations. Combined together, these limitations render the current results preliminary and not fully conclusive. The study’s major shortcomings are worthy of mention, as they may serve as a guide for interpreting results and designing future trials.

First, the overall number of convenience-sampled subjects was low, and the accrual period was lengthy. With findings of no significant differences between the FBT and OXY subjects in any endpoint (including undesirable outcomes), the current data are quite suggestive of between-group similarity. However, with more subjects the point-estimates’ precision would be greater and associated CIs narrower. With wide CIs, there is no ability to use the study results to draw definitive, concrete conclusions.

Slow rates of study accrual were due to a variety of factors, not least of them the requirement for potential study subjects to agree to stay up to two hours post-study entry. This was explicitly required as part of the regulatory framework of administering a potent opioid to opioid-naı¨ve ED patients, and in fact the prolonged observation did in fact provide useful evidence of the safety of administering 200 mcg FBT.

While some of the factors accounting for slow study case accrual were amenable to intervention (e.g. changing the observation period from two hours to one hour post-study entry), others (e.g. availability of dedicated research assistants) remained problematic. The study’s use of convenience sampling, which always predisposes to selection bias, is particularly likely to restrict conclusions and external validity. While the FBT and OXY groups were statistically similar, the results of the study are best extrapolated only to patients with similar profile (including willingness to be observed for prolonged periods).

Another study limitation was the selection of the FBT dosage to be tested. The rough equivalence of 200 mcg FBT with 10 mg oxycodone is supported by previous study in the ED and the available pharmacologic information. However, the approximate equivalence is just that, an approximation. It leaves room for potential for an increased dose of FBT as being both safe and effective; this potential may need to be studied if there is follow-up assessment of FBT in the ED. Of course, increasing the dosage of FBT has just as much chance of increasing side effects, as it does of increasing analgesic efficacy, so the question of higher-dose FBT must be addressed prospectively before this approach can be recommended.

An additional limitation lay in the methods for assessing pain intensity. The NPRS used is a standard tool in the ED, and the two-point movement defined a priori as representing significant pain relief has been recommended by experts and used in previous ED studies. However, it is possible that a smaller, but still significant, degree of pain relief difference could have been detected if there were a more precise measurement of patients’ pain. Furthermore, some clinicians may judge that there are other mechanisms for adjudicating pain relief, that are preferable to the use of the NPRS drop of two points. Nonetheless, the fact that the two-point definition of significant pain reduction failed to identify an intergroup difference is indeed suggestive that no substantial difference between FBT and OXY subjects’ pain relief was present.

Additional limitations in extrapolating the results lie in the fact that the oxycodone preparation that was received by OXY patients also received an additional analgesic, acetaminophen. Since the combined-drug preparation is that which is used nearly exclusively in the study ED, it was most practical and appropriate to use the combination therapy for the “oxycodone” subjects in this study. However, the interpretation of this study’s results should reflect its comparison of single-drug therapy with fentanyl, against dual-drug therapy with oxycodone and acetaminophen.

As a final note of caution, the current study is not intended to address the complicated clinical question of balancing need to avoid oligoanalgesia, against the need to avoid inappropriate use of opioids. The decision as to which patients should receive opioid therapy for musculoskeletal injuries is important, but it is not the focus of the current investigation.

CONCLUSION

In conclusion, this analysis of transbuccal fentanyl (200 mcg) versus oral oxycodone (10 mg, with 650 mg acetaminophen) failed to show any statistically or clinically significant difference in analgesic efficacy, speed of pain reduction, side effect occurrence, or overall patient preference. The role, if any,
of transbuccal fentanyl in the ED remains to be defined, in larger trials (that may include non-inferiority approaches). Further investigations should incorporate a rough analgesic equivalence between 200 mcg FBT and 10 mg oxycodone with 650 mg acetaminophen. The results of this trial may be useful in enabling sample size calculations for further study.

**Author contributions**

Authors ST and AA both contributed to conception and design of the study. Author NB contributed to data analysis and interpretation. Author SM contributed to acquisition and interpretation of data. All authors participated in drafting of the manuscript (including revisions). All authors read and approved the final manuscript.

**Competing interests and funding**

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**Prior presentation**

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**REFERENCES**


