ORIGINAL ARTICLE

Fentanyl Buccal Tablet: A New Breakthrough Pain Medication in Early Management of Severe Vaso-Occlusive Crisis in Sickle Cell Disease

Lucia De Franceschi, MD*; Paolo Mura, MD†; Vittorio Schweiger, MD‡; Elisa Vencato, MD*; Francesca Maria Quaglia, MD*; Letizia Delmonte, MD*; Maurizio Evangelista, MD§; Enrico Polati, MD‡; Oliviero Olivieri, MD*; Gabriele Finco, MD†

*Department of Medicine, Section of Internal Medicine, University of Verona-AOUI-Verona, Verona; †Department of Medical Science "M. Aresu", Section of Anesthesia, Intensive Care and Pain Therapy, University of Cagliari, Cagliari; ‡Department of Surgical Science, Anesthesiology, Intensive Care and Pain therapy Center, University of Verona-AOUI-Verona, Verona; §Department of Emergency, Institute of Anesthesia, Resuscitation and Pain Medicine, Catholic University of Sacred Heart, Rome, Italy

■ **Abstract**

Background: Sickle cell disease (SCD) is a worldwide distributed hereditary red cell disorder. The principal clinical manifestations of SCD are the chronic hemolytic anemia and the acute vaso-occlusive crisis (VOCs), which are mainly characterized by ischemic/reperfusion tissue injury. Pain is the main symptom of VOCs, and its management is still a challenge for hematologists, requiring a multidisciplinary approach.

Methods: We carried out a crossover study on adult SCD patients, who received two different types of multimodal analgesia during two separate severe VOCs with time interval between VOCs of at least 6 months. The first VOC episode was treated with ketorolac (0.86 mg/kg/day) and tramadol (7.2 mg/kg/day) (TK treatment). In the second VOC episode, fentanyl buccal tablet (FBT; 100 μg) was introduced in a single dose after three hours from the beginning of TK analgesia (TKF treatment). We focused on the first 24 hours of acute pain management. The primary efficacy measure was the time-weighted-sum of pain intensity differences (SPID24). The secondary efficacy measures included the pain intensity difference (PID), the total pain relief (TOTPAR), and the time-wighted sum of anxiety (SAID24).

Results: SPID24 was significantly higher in TKF than in TK treatment. All the secondary measures were significantly ameliorated in TKF compared to TK treatment, without major opioid side effects. Patients satisfaction was higher with TKF treatment than with TK one.

Conclusions: We propose that VOCs might require breakthrough pain drug strategy as vaso-occlusive phenomena and enhanced vasoconstriction promoting acute ischemic pain component exacerbate the continuous pain of VOCs. FBT might be a powerful and feasible tool in early

Address correspondence and reprint requests to: Paolo Mura, MD, Department of Medicine, Section of Anesthesia, Intensive Care and Pain Therapy; University of Cagliari, AOU Cagliari, Policlinico "Duilio Casula", SS554 Bivio per Sestu, 09042 Monserrato (CA), Italy. E-mail: mura_paolo@hotmail.com.

Submitted: October 1, 2014; Revision accepted: March 24, 2015
DOI. 10.1111/papr.12313

© 2015 World Institute of Pain, 1530-7085/16/$15.00

management of acute pain during VOCs in emergency departments. ■

Key Words: opioids, breakthrough pain, pain service, acute, vaso-occlusive crisis, sickle cell disease, fentanyl, buccal administration, transmuccosal

INTRODUCTION

Sickle cell disease (SCD) is a worldwide distributed hereditary red cell disorder characterized by the synthesis of pathological hemoglobin S (HbS).[1, 2] The principal clinical manifestations of SCD are chronic hemolytic anemia and acute vaso-occlusive crisis (VOCs), which are related to ischemic/reperfusion tissue injury.[1, 3, 4] SCD patients are the major users of emergency departments (EDs) compared to subjects with other severe hemoglobinopathies due to VOCs.[5] Pain is the main symptom of VOCs, and its management is still a challenge for hematologists, requiring a multidisciplinary approach.[6] Although protocols for control of acute pain in SCD have been developed in the last decade,[6–10] SCD patients still feel undertreated.[11] Different mechanisms are involved in pain generation during VOCs: (i) the ischemic/reperfusion injury and activation of inflammatory response; (ii) the local release of sensitizing mediators, contributing to local vasodilation and edema; (iii) the neuropathic component sustained by an aberrant stimulation of central and peripheral nervous system.[6] Pain treatment with either nonsteroidal anti-inflammatory drugs (NSAID), such as ketoprofen,[12] or morphine[13, 14] is partially successful in management of VOCs, suggesting that the biocomplexity of pain origin in SCD requires a multitarget pharmacological approach. Recently, we reported that multimodal analgesia with ketorolac, a NSAID, and tramadol, an atypical opioid, is effective in management of acute pain during severe VOCs.[15] Multimodal analgesia is largely used in pain control related to major surgery or to chronic pain and is based on the co-administration of drugs with different pharmacological mechanisms, controlling pain of multiple origins.[16, 17] In SCD, early studies on pain management during VOCs have shown that fast-acting opioids such as fentanyl might be an interesting therapeutic tool when associated to major opioids.[18–20] However, its route of administration has largely limited fentanyl introduction in routine protocols for acute pain control in SCD. The recent development of rapid-onset fentanyl formulations that use less invasive delivery such as oral mucosa has allowed the introduction of fentanyl for management of acute pain of cancer and noncancer origin.[10, 21–23] Among the rapid-onset fentanyl formulations, FBT seems to be a feasible tool as breakthrough pain (BTP) drug in treatment of acute pain in ED.[18, 22]

METHODS

Study Design

This is a crossover clinical study on a group of adult patients with SCD referred to the Department of Medicine, University of Verona, Italy, between January 2010 and July 2013. The study was carried out according to the guidelines of the local ethical committee. Each patient was informed on the ongoing study, and written informed consent was obtained. Data were anonymously collected. The study involved SCD patients aged 18–45 years with severe painful VOCs, defined as bone pain (ie, extremities, hips, or back) or abdominal pain, for which no other clinical explanation was identified, with a visual analogue scale pain level (VAS) of 7 or more. Each hospitalization was defined as an episode of VOC.[15] Patients were not considered if they had a history of opioid consumption during the 2 weeks before the VOC. Other exclusion criteria were contraindication to opioids administration (such as a history of opioids misuse and abuse), altered conscious state, pregnancy or lactating, hepatic and/or renal failure, gastritis or peptic ulcer, allergies, or other contraindications to any ingredient in the study drugs. The presence of cardiopulmonary disease, medical, or psychiatric disease that, in the opinion of the investigators, might compromise the collection of the study data were also exclusion criteria.

Study Procedures

At the admission to our Department, two physicians independently evaluated the SCD patients and attributed a clinical level of pain severity and pain localization. When the VAS pain score was 7 or more, the VOC event was defined as severe pain VOC episode.[15, 24] We carried out a power analysis for this study, and we identified a number of 19 to demonstrate with a 0.8 power and a level of significance of 0.05 a reduction in VAS of at least 1.3 when FBT is added to standard treatment on control of acute pain in SCD. This prediction is in agreement with a previous report.[25] Here, we studied 20 SCD patients, who received two

different types of analgesic treatment during two separate VOCs with time interval between VOCs of at least 6 months. The multimodal analgesic treatment was started in both groups within 1 hour from the arrival in the ED. In the first VOC episode, pain management was performed by multimodal analgesia with administration of a continuous intravenous infusion of ketorolac (0.86 mg/kg/day), tramadol (7.2 mg/kg/day), and metoclopramide (0.57 mg/kg/day) for a maximum of 72 hours (TK treatment). In the second group of treatment ($n = 20$), pain management was performed by multimodal analgesia with the administration of the same pharmacological protocol with the addition of fentanyl buccal tablet (FBT) 100 μg in single administration after three hours from the beginning of multimodal analgesia (TKF treatment). FBT was repeatable if requested by the patient due to insufficient analgesia, from 30 minutes after the first dose to a maximum cumulative dosage of 400 μg/24 hours. In respect to various fast-acting formulations of oral fentanyl, FBT was chosen because it seems to reach a higher plasma concentrations compared to other fentanyl preparations such as oral transmucosal fentanyl citrate (OTFC).[20] During each VOC episode, pain intensity was recorded using an 11-point pain scale (visual analogue scale, VAS) at admission and at 3, 6, 12, 18, and 24 hours from the beginning of each treatment. At the same time intervals, we also evaluated (i) patients pain relief (PR) with a scale from 0 (no PR) to 10 (complete PR); (ii) the level of anxiety with a scale from 0 (no anxiety) to 10 (the worst possible anxiety); (iii) patients mood level with a scale from 0 (worst mood) to 10 (best mood); iv) patients sedation level with a scale from 0 (deep sedation) to 10 (no sedation). The primary efficacy measure was the time-weighted sum of pain intensity differences from 3 to 24 hours after the administration of the drugs (time-weighted $SPID_{24}$). The PID (pain intensity difference) was calculated at each time interval by subtracting the baseline from the actual pain intensity score. $SPID_{24}$ was derived as follows:

$$SPID_{24} = \sum [T_{(i)} - T_{(i-1)}] \times PID_{(i)}$$

where $T_{(i)}$ is the scheduled time, and $PID_{(i)}$ is the PID score at time i. The secondary efficacy measure was time-weighted total pain relief (TOTPAR), calculated considering painrRelief (PR) instead of PID. Changes in patient's anxiety during treatment was evaluated as time-weighted $SAID_{24}$ (sum of anxiety intensity differences from 3 to 24 hour) calculated in the same way as $SPID_{24}$. The type and the duration of analgesic therapy as well as the number of additional doses of FBT were recorded. The safety and tolerability profile of the treatments were assessed based on possible adverse effects (AEs) reported by the patients and recorded by the investigators as previously reported.[15] Despite the availability of specific and reliable questionnaires aimed to assess drug side effects in chronic pain,[26] equivalent tools to be used in acute pain in the context of emergency departments are not present. Thus, we chose to rely on patient report and usual clinical and instrumental monitoring as deemed appropriate for this kind of therapy. The incidence of nausea or vomiting, sedation, respiratory distress, and renal failure was actively searched by the investigators. In particular, arterial peripheral oxygen saturation ($SpO_{2\%}$) was measured by a pulse oximeter (SATLITE-TRans®, Datex, Helsinki, Finland) at the admission and at the different time points. Patients were asked to quantitate nausea and sedation on a 10-point scale. At 72 hours, patients satisfaction about the treatment was collected using a five-point scale (0 not satisfied, 1 partially satisfied, 2 satisfied enough, 3 adequately satisfied, and 4 fully satisfied). Data were collected by blinded physicians and nurses.

Statistical Analysis

The statistical analysis was performed comparing data from the two treatments of patients with VOC. As no data followed Gaussian distribution (as tested with Kolmogorov Smirnov) nor standard deviations were consistently equal (as tested with Bartlett), nonparametric statistics were implemented. The evaluation of treatment's efficacy, tolerability, and safety ($SPID_{24}$ and other cumulative calculated measures) was performed using the two tailed Wilcoxon signed-rank test comparing the two treatments. Friedman's nonparametric test for related samples followed by Dunn correction for multiple comparisons was used to compare the time course for each parameter at each interval. A P value < 0.05 was considered statistically significant. Descriptive statistics were reported in terms of medians and interquartile range (IQR) for quantitative variables and in terms of absolute frequencies and percentages for qualitative variables. Statistical analysis was performed using MedCalc for Windows, version 11.3.0.0 (MedCalc Software®, Ostend, Belgium) and GraphPad Prism® for Windows, version

5.01 and 6.01 (GraphPad® Software, San Diego, CA, USA).

RESULTS

In this study, we evaluated the impact of FBT as breakthrough pain medication in the early phase of pain management during severe VOCs in adult patients with SCD. We treated 20 SCD patients during 2 separate severe VOC episodes in the time interval of the study. The demographic, hematological, and biochemical characteristics of SCD patients on steady state and at the admission to the hospital for acute severe VOCs are reported in Table 1. A large portion of patients were homozygous for HbS (SS). At baseline (steady state), patients demonstrated chronic hemolytic anemia (Hb median 11 g/dL; LDH median 484 U/L) in the absence of inflammatory signs (Table 1). At admission to the ED for acute severe VOCs, the pain localization referred by patients was similar in both VOC episodes and in agreement with previous report by McClish et al.[27] A significant reduction in Hb levels (Hb median 8 g/dL) compared to steady state and increased LDH levels (median 750 and 698 U/L) associated with inflammatory response (C-reactive protein, CRP median 23 and 28 mg/dL) were observed in SCD patients (Table 1). In each VOCs, we focused on the first 24 hours after patient admission to ED to evaluate the efficacy of analgesia with and without FBT associated with multimodal analgesia.

In both TK and TKF treatments, the VAS pain was significantly reduced at 6 hours, reaching a plateau thereafter in TK treatment (Figure 1A). In TKF treatment, the VAS pain – markedly reduced at 6 hours – was significantly and continuously lower compared to TK at 6 and 12 hours of treatment (Figure 1A). All TFK patients had a reduction in VAS greater than 30% both at 6 and 12 hours, while only one patient (5%) had a 30% reduction at 6 hours and 4 (20%) at 12 hours in TK group. A 50% reduction in pain intensity was present in 12 (at 6 hours) and 18 (at 12 hours) in TFK group. No patient had such reduction in VAS in TK treatment. The differences in proportions were statistically significant (Fisher exact test $P < 0.0001$). VAS pain relief was higher in TKF compared to TK treatment following FBT administration, with $P < 0.0001$ at 6 and $P = 0.0213$ at 24 hours, and only slightly higher (0.070) at 18 hours (Figure 2A). The time-weighted TOTPAR as secondary efficacy measurement of FBT clinical impact was significantly lower in TK compared to TKF treatment (TK *vs* TKF, $P < 0.0001$). The reduction in pain intensity assessed by PID was significantly higher in TKF compared to TK treatment at 6 and 12 hours, of treatment (and P for increase at 18 hours was 0.07), suggesting a clinical improvement of pain control in TKF compared to TK one (Figures 1A, 2B). $SPID_{24}$, as primary efficacy measurement, was significantly higher in SCD patients treated with TKF than with TK (TK *vs* TKF, $P < 0.0001$). Due to insufficient analgesia, two of 20 SCD patients required a second administration of FBT at 30 minutes after the first one; both patients were homozygous for HbS.

During VOCs, we evaluated the impact of FBT on patients' anxiety. As shown in Figure 3(A), the reduction of patients' anxiety was higher in TKF compared to TK treatment. The SAID24, as secondary efficacy measurement, was significantly lower in TK treatment compared

Table 1. Patients Characteristics on Steady State and at the Hospital Admission for Severe VASO-Occlusive Crisis (VOCs)

Parameters	Patients ($n = 20$)		
Age (years)	22 (17.0 to 28.0)		
Gender (M/F)	9/11		
SS/βS	16/4		
On HU	12/20		
	Steady state ($n = 20$)	Admission for VOCs (TK; $n = 20$)	Admission for VOCs (TKF; $n = 20$)
Hb (g/dL)	11 (9.0 to 11.7)	8 (6.7 to 9)*	8 (6.5 to 8.9)*
Creatinine (mg/dL)	0.7 (0.3 to 1.5)	1.2 (0.9 to 1.8)	1.1 (0.9 to 1.4)
LDH (U/L)	484.0 (310.2 to 1104.2)	750 (512 to 982)*	698 (505 to 897)*
Albumine (g/L)	44.3 (35.6 to 49.7)	48 (46 to 51)	49 (46 to 53)
CRP (mg/L)	3.0 (1.0 to 15.8)	23 (17 to 28)*	28 (16 to 29)*
Pain site(s) during VOCs	–	80% of the pts: low back 10% of pts: extremities 10% of the pts: thorax	70% of the pts: low back 18% of pts: extremities 12% of the pts: thorax
Duration of hospitalization (days)	–	4.5 ± 0.8	3.8 ± 1.2

Data are expressed as median (range). M, male; F, female; Hb, hemoglobin; HbS, sickle hemoglobin; HbF, fetal hemoglobin; LDH, lactate dehydrogenase; CRP, C-reactive protein; TK, tramadol plus ketorolac group; TKF, pts: patients; tramadol plus ketorolac plus fentanyl buccal tablet treatment; *$P < 0.05$ compared to steady state.

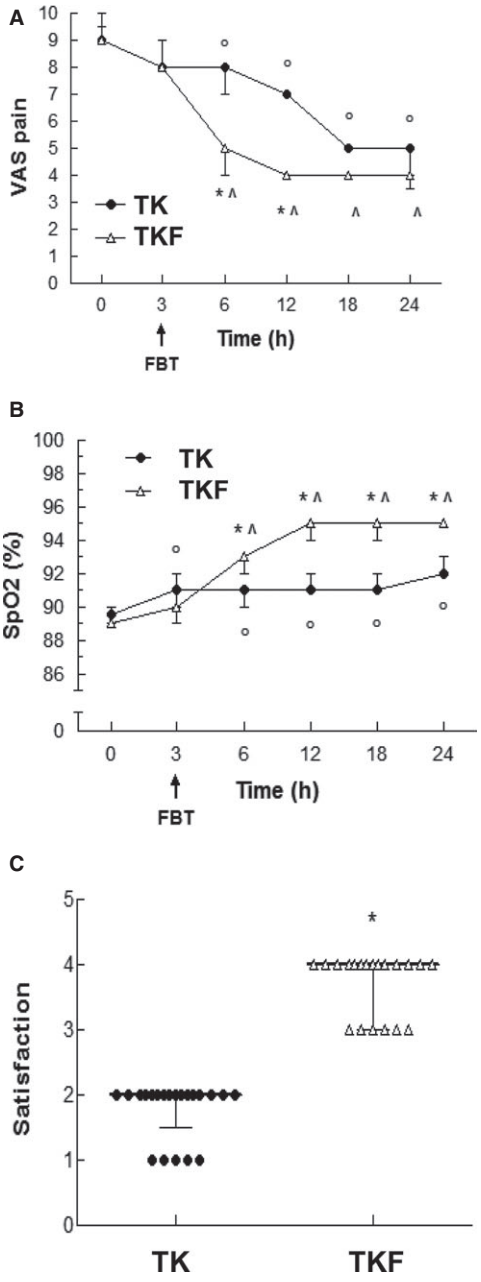

Figure 1. Time course of (A) VAS pain, (B) median SpO2 (%), and (C) patients' satisfaction of pain treatment for SCD patients treated with either TK: tramadol (7.2 mg/kg/day) and ketorolac (0.86 mg/kg/day) or TKF: tramadol (7.2 mg/kg/day), ketorolac (0.86 mg/kg/day) and fentanyl buccal tablet (FBT, 100 μg). Data are expressed as median and interquartile range ($n = 20$ each treatment; °$P < 0.05$ compared to time 0 in TK treatment; ^$P < 0.05$ compared to time 0 in TKF treatment; *$P < 0.05$ TK vs TKF treatment at the different time points). The arrow indicates when FBT was administrated in TKF treatment. Patients' satisfaction was recorded at 72 hours with a five-point scale (0 not satisfied, 1 partially satisfied, 2 satisfied enough; 3 adequately satisfied, and 4 fully satisfied) for the two investigational treatments: The horizontal line for each group represents the median value, and the vertical bars represent the interquartile range ($n = 20$ each group; *$P < 0.05$ compared to TK treatment).

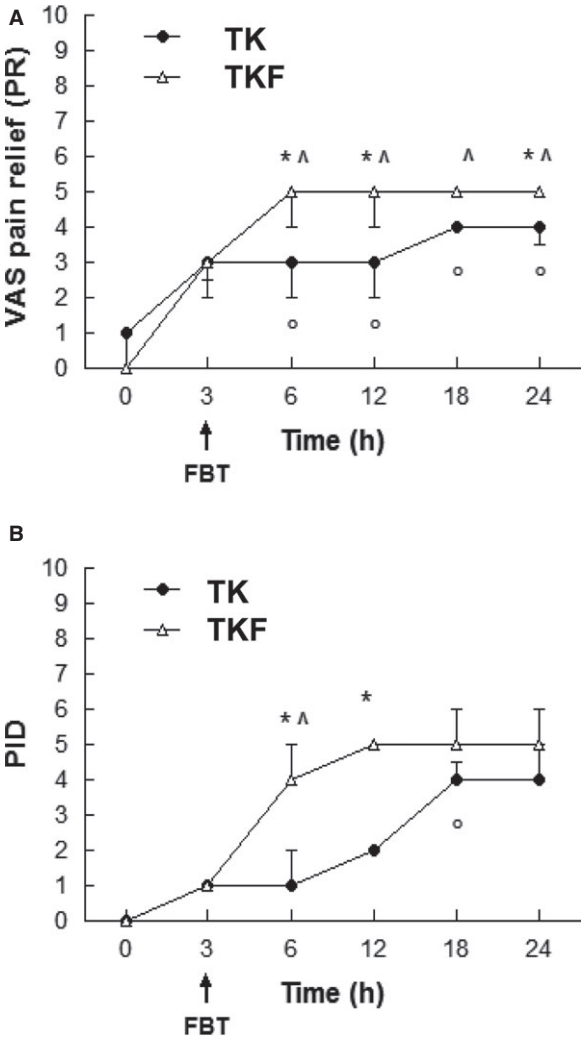

Figure 2. VAS Pain Relief and PID. ($n = 20$ each treatment; °$P < 0.05$ compared to time 0 in TK treatment; ^$P < 0.05$ compared to time 0 in TKF treatment; *$P < 0.05$ TK vs TKF treatment at the different time points).

to TKF, indicating the clinical efficacy of FBT on patients' anxiety (TK *vs* TKF, $P < 0.0001$). As the acute pain during VOCs is inscribed in chronic pain experience, which affects pain memories and global emotional insights of SCD patients,[7,8] we evaluated patients' mood during the analgesic treatments. We found that VAS patients' mood was significantly greater in TKF than in TK treatment at 6, 12, and 18 hours of study (Figure 3B) and nearly significantly greater at 24 hours ($P = 0.06$).

During analgesic treatment, we evaluated patients' sedation as a possible opioid-related side effect. In TKF-treated SCD patients, sedation was greater than in TK treatment at 6 hours and 12 hours, while no significant differences were observed at 18 and 24 hours (Figure 3C).

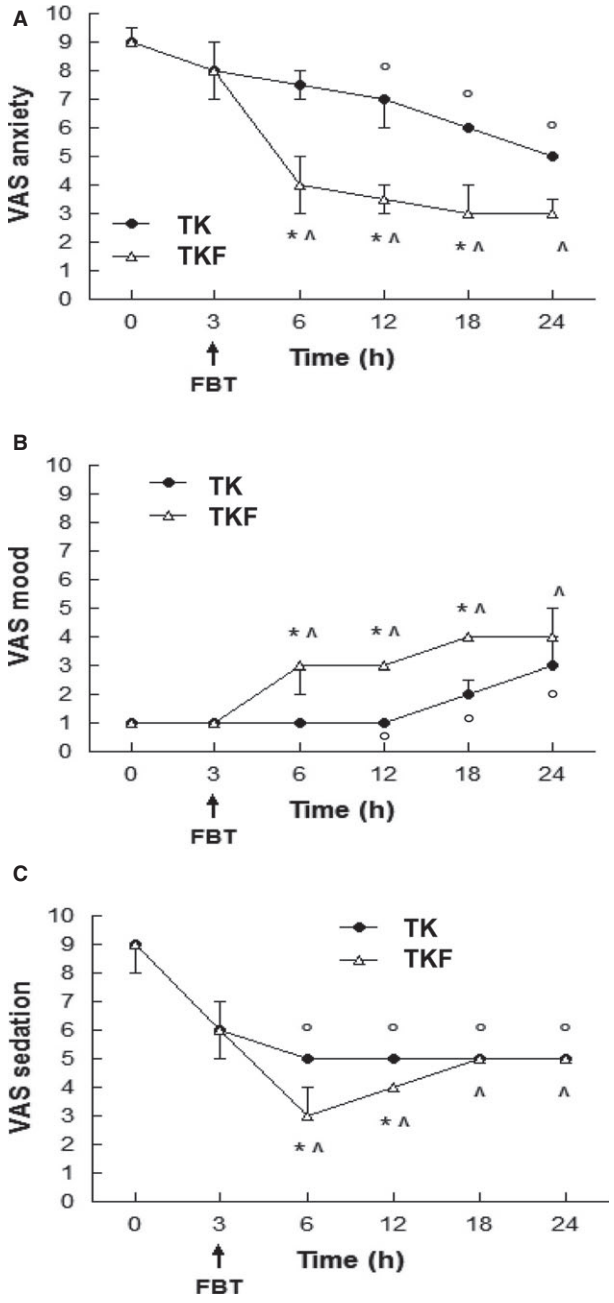

Figure 3. VAS. Anxiety – Mood – Sedation ($n = 20$ each treatment; °$P < 0.05$ compared to time 0 in TK treatment; ^$P < 0.05$ compared to time 0 in TKF treatment; *$P < 0.05$ TK vs TKF treatment at the different time points).

We then evaluated the peripheral oxygen saturation (SpO_2%) in TK and TKF treatment as reduced peripheral oxygen saturation (SpO_2) and alveolar ventilation have been described in SCD patients during severe VOCs[28](Needleman et al., 2002). As shown in Figure 1(B), SpO2 levels were significantly higher in TKF than in TK treatment at 6, 12, 18, and 24 hours of study. No major side effects were recorded either in TK- or TKF-treated SCD patients. In particular, no nausea, vomit, or respiratory depression episodes were recorded. We also collected data on patients' satisfaction during TK and TKF treatment. As shown in Figure 1(C), we found that patients' satisfaction was greater in TKF than in TK treatment. We did not find significant differences in time of hospitalization between TKF and TK treatment as shown in Table 1.

DISCUSSION

The control of acute pain in the early phase of severe VOCs is still unsatisfactory and negatively impacts SCD patients' quality of life.[7, 8, 29] The acute pain of VOCs is generally managed with increasing or rescue dose of around-the-clock medication such as oral morphine.[6] However, studies in both human subjects and mouse models for SCD have shown that treatment with morphine is associated with increase rate of acute chest syndrome, renal toxicity, and peripheral system dysfunction.[6] In addition, the accelerated clearance of morphine observed in SCD patients requires the development of alternative or additional therapeutic strategies in controlling acute pain of VOCs.[30–32] In SCD, VOCs are characterized by severe continuous pain with exacerbation of acute pain most likely due to sudden temporary local enhanced vasoconstriction phenomena that are favored by abnormal parasympathetic vascular response, promoting acute ischemic pain.[33,34] The temporal characteristics, the intensity, and the mechanism of this type of pain might be considered as a breakthrough pain as defined by the literature[35] (Davies et al., 2009) (Figure 2). Here, we show that FBT used as breakthrough pain medication significantly improved pain relief during early phase of severe VOCs in adult patients with SCD. This finding is important as the adequate and early control of acute pain in VOCs might reduce more severe sickle cell-related complications.[6] The increase in SPID24, as primary efficacy measure, and in TOTPAR (total pain relief), as secondary efficacy measure, validates the clinical improvement of pain management with FBT associated with the infusion of ketorolac and tramadol (TK) in the early phase of VOCs. Indeed, the reduction in VAS pain was maintained from 6 to 24 hours after FBT administration, without hyperalgesia, acute tolerance, or blunted response.[6, 22]

These findings might be related to the pharmacologic characteristics of oral fentanyl, which becomes rapidly bioavailable at high plasma concentration, bypassing

the cytochrome P450 metabolism.[20, 21] In addition, oral mucosa as route of drug delivery offers clear advantages compared to other fentanyl formulations in the context of patients management in EDs.[22,36] Although one limitation of the present study is that it is not randomized, the sample size is appropriated to evaluate the clinical impact of FBT on acute pain control in SCD, based on the recently reported power analysis on the use of intranasal fentanyl for acute pain control in children with SCD.[25] The additional observation that SAID24 (sum of anxiety Intensity differences), as secondary efficacy measure, was increased in TKF treatment and was paralleled with an amelioration of patients mood supports the clinical importance of FBT associated with multimodal analgesia in treatment of acute pain related to VOCs. The SCD patients' satisfaction was higher in TKF than in TK treatment, in agreement with other reports in cancer and noncancer pain origin.[20, 37] It is of interest to note that the improved pain control obtained with FBT in the TKF treatment, resulted in significant amelioration of the peripheral oxygen, suggesting an improvement of gas exchange in the presence of an optimized pain control.[28]

Based on these data, we postulated that pain crisis in SCD are characterized by continuous pain with exacerbated acute pain related to the dynamic vaso-occlusive phenomena that are negatively affected by enhanced vasoconstriction, requiring a breakthrough pain medication strategy (Figure 2). Our results are also supported by a recent communication on the use of intranasal fentanyl in management of acute pain in pediatric sickle cell patients (B.T. Akinsola, R. Hagbom, A. Zmitrovich, P. Kavanagh, A. Ashkouti, A. Fletcher, N. Vinson, H. Simon, H. Fleming, S. Jain, O. Adisa, C. Dampier, C.R. Morris, 2014, abstract presented at the 56th ASH Annual Meeting in San Francisco). There are some limitations of the present study mainly related to the absence of a placebo control group. However, our data together with the recent report by Akinsola generate the preliminary evidence for the use of FBT in management of acute VOCs in SCD, which will be further investigated in larger multicenter study.

Thus, we suggest FBT as BTP drug might be a powerful and feasible tool in early management of acute pain in ED as reported in other acute noncancer pain.[22] Future studies should be carried out to further evaluate the impact of FBT on acute pain management in EDs in a large cohort of SCD patients.

DISCLOSURES

The Authors have no potential conflict to disclose.

AUTHORS CONTRIBUTIONS

GF and LDF designed the study; FMQ, EV, and LD collected the data; VS, GF, LDF, PM, and ME analyzed the data; LDF, GF, VS, and PM wrote the article; OO and EP contributed to article discussion.

REFERENCES

1. De Franceschi L, Cappellini MD, Olivieri O. Thrombosis and sickle cell disease. *Semin Thromb. Hemost.* 2011;37:226–236.

2. De Franceschi L, Corrocher R. Established and experimental treatments for sickle cell disease. *Haematologica*. 2004;89:348–356.

3. Vinchi F, De Franceschi L, Ghigo A, et al. Hemopexin therapy improves cardiovascular function by preventing heme-induced endothelial toxicity in mouse models of hemolytic diseases. *Circulation*. 2013;127: 1317–1329.

4. De Franceschi L, Saadane N, Alper SL, Brugnara C, Beuzard Y. Treatment with oral clotrimazole blocks Ca^{2+}activated K^+ transport and reverses erythrocyte dehydration in transgenic SAD mice: model for therapy of sickle cell disease. *J. Clin. Invest.* 1994;93:1670–1676.

5. Carroll CP, Haywood C Jr, Fagan P, Lanzkron S. The course and correlates of high hospital utilization in sickle cell disease: evidence from a large, urban Medicaid managed care organization. *Am. J. Hematol.* 2009;84:666–670.

6. Ballas SK, Gupta K, Adams-Graves P. Sickle cell pain: a critical reappraisal. *Blood*. 2012;120:3647–3656.

7. Anie KA, Grocott H, White L, Dzingina M, Rogers G, Cho G. Patient self-assessment of hospital pain, mood and health-related quality of life in adults with sickle cell disease. *BMJ Open*. 2012;2:e001274.

8. Anie KA, Steptoe A. Pain, mood and opioid medication use in sickle cell disease. *Hematol. J.* 2003;4:71–73.

9. Benjamin L. Pain management in sickle cell disease: palliative care begins at birth? *Hematology Am. Soc. Hematol. Educ. Program* 2008;1: 466–474.

10. Dampier CD, Smith WR, Kim HY, et al. Opioid patient controlled analgesia use during the initial experience with the IMPROVE PCA trial: a phase III analgesic trial for hospitalized sickle cell patients with painful episodes. *Am. J. Hematol.* 2011;86:E70–E73.

11. Haywood C Jr, Beach MC, Lanzkron S, et al. A systematic review of barriers and intervent to improve appropriate use of therapies for sickle cell disease. *J. Natl Med. Assoc.* 2009;101:1022–1033.

12. Bartolucci P, El Murr T, Roudot-Thoraval F, et al. A randomized, controlled clinical trial of ketoprofen for sickle-

cell disease vaso-occlusive crises in adults. *Blood*. 2009;114:3742–3747.

13. Ballas SK. Sickle cell disease: current clinical management. *Semin. Hematol.* 2001;38:307–314.

14. Van Beers EJ, Van Tuijn CF, Nieuwkerk PT, Friederich PW, Vranken JH, Biemond BJ. Patient-controlled analgesia versus continuous infusion of morphine during vaso-occlusive crisis in sickle cell disease, a randomized controlled trial. *Am. J. Hematol.* 2007;82:955–960.

15. De Franceschi L, Finco G, Vassanelli A, Zaia B, Ischia S, Corrocher R. A pilot study on the efficacy of ketorolac plus tramadol infusion combined with erythrocytapheresis in the management of acute severe vaso-occlusive crises and sickle cell pain. *Haematologica*. 2004;89:1389–1391.

16. Ambrosio F, Finco G, Mattia C, et al. SIAARTI recommendations for chronic noncancer pain. *Minerva Anestesiol.* 2006;72:859–880.

17. Raffa RB, Friderichs E, Reimann W, et al. Complementary and synergistic antinociceptive interaction between the enantiomers of tramadol. *J. Pharmacol. Exp Ther.* 1993;267:331–340.

18. Arthur AO, Holder P. A review of transbuccal fentanyl use in the emergency department. *Pain Res. Treat.* 2012;2012:768796.

19. Paech MJ, Bloor M, Schug SA. New formulations of fentanyl for acute pain management. *Drugs Today (Barc)* 2012;48:119–132.

20. Smith H. A comprehensive review of rapid-onset opioids for breakthrough pain. *CNS Drugs* 2012;26:509–535.

21. Darwish M, Hamed E, Messina J. Fentanyl buccal tablet for the treatment of breakthrough pain: pharmacokinetics of buccal mucosa delivery and clinical efficacy. *Perspect. Medicin. Chem.* 2010;4:11–21.

22. Osborne V, Layton D, Fogg C, Al-Shukri M, Shakir SA. Utilization of fentanyl buccal tablets in England: exploring off-label use reported in a cohort study. *Eur. J. Pain.* 2014;18:506–512.

23. Smith HS. Considerations in selecting rapid-onset opioids for the management of breakthrough pain. *J. Pain Res.* 2013;6:189–200.

24. Forni GL, Finco G, Graziadei G, et al. Development of interactive algorithm for clinical management of acute events related to sickle cell disease in emergency department. *Orphanet J Rare Dis.* 2014;9:91.

25. Barrett MJ, Cronin J, Murphy A, et al. Intranasal fentanyl versus intravenous morphine in the emergency department treatment of severe painful sickle cell crises in children: study protocol for a randomised controlled trial. *Trials*. 2012;13:74.

26. Jonsson T, Christrup LL, Højsted J, et al. Symptoms and side effects in chronic non-cancer pain: patient report vs. systematic assessment. *Acta Anaesthesiol. Scand.* 2011; 55: 69–74.

27. McClish DK, Smith WR, Dahman BA, et al. Pain site frequency and location in sickle cell disease: the PiSCES project. *Pain*. 2009;145:246–251.

28. Needleman JP, Benjamin LJ, Sykes JA, Aldrich TK. Breathing patterns during vaso-occlusive crisis of sickle cell disease. *Chest*. 2002;122:43–46.

29. Anie KA, Green J. Psychological therapies for sickle cell disease and pain. *Cochrane Database of Syst. Rev.* 2012;2: CD001916.

30. Darbari DS, Neely M, Van den Anker J, Rana S. Increased clearance of morphine in sickle cell disease: implications for pain management. *J. Pain.*2011;12:531–538.

31. Dampier CD, Setty BN, Logan J, Ioli JG, Dean R. Intravenous morphine pharmacokinetics in pediatric patients with sickle cell disease. *J. Pediatr.* 1995;126:461–467.

32. Nagar S, Remmel RP, Hebbel RP, Zimmerman CL. Metabolism of opioids is altered in liver microsomes of sickle cell transgenic mice. *Drug Metab Dispos.* 2004;32:98–104.

33. Juncos R, Juncos L, Hebbel RP, Vercellotti GM, Katusic ZS, Nath KA. Selective enhancement of contractions to alpha1-adrenergic receptor activation in the aorta of mice with sickle cell disease. *J. Cardiovasc Pharmacol.* 2011;57:263–266.

34. Sangkatumvong S, Khoo MC, Kato R, et al. Peripheral vasoconstriction and abnormal parasympathetic response to sighs and transient hypoxia in sickle cell disease. *Am. J Respir. Crit. Care Med.* 2011;184:474–481.

35. Davies AN, Dickman A, Reid C, Stevens AM, Zeppetella G. The management of cancer-related breakthrough pain: recommendations of a task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. *Eur. J. Pain.* 2009;13:331–338.

36. Nicolazzo JA, Reed BL, Finnin BC. Buccal penetration enhancers–how do they really work? *J. Control. Release.* 2005;105:1–15.

37. Fine PG, Messina J, Xie F, Rathmell J. Long-term safety and tolerability of fentanyl buccal tablet for the treatment of breakthrough pain in opioid-tolerant patients with chronic pain: an 18-month study. *J. Pain Symptom. Manage.* 2010;40:747–760.