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BRIEF ARTICLE

Tramadol use in pediatric sickle cell disease patients with vaso-occlusive crisis

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Abstract

AIM: To evaluate whether the addition of scheduled oral tramadol to intravenous morphine and intravenous ketorolac reduces morphine requirements.

METHODS: This single-centered, Institutional Review Board-approved, retrospective study at Moses Cone Memorial Hospital included pediatric patients who were ⩾ 2 years old with vaso-occlusive crisis (VOC) caused by sickle cell disease (SCD), were on morphine patient-controlled analgesia (PCA), and had scheduled oral tramadol added to their standard pain regimen. The study population was admitted between March 2008 and March 2011. The data was collected from electronic records and included age, weight, morphine use, tramadol use, hemoglobin, pain scores, number of days on PCA, length of hospital stay, respiratory rate, and polyethylene glycol use. Thirty patients were analyzed as independent admissions and seven patients as paired admissions.

RESULTS: Eighteen pediatric SCD patients with VOC received morphine PCA and intravenous ketorolac and twelve patients received morphine PCA and intravenous ketorolac and scheduled oral tramadol. Baseline characteristics were similar between both groups with the exception of the average weight, which was greater in the tramadol group than in the morphine group. The average morphine requirements in patients with and without the use of tramadol were similar, both for the independent admissions [0.58 mg/kg per day *vs* 0.65 mg/kg per day (P = 0.31)] and the paired admissions [0.71 mg/kg per day *vs* 0.77 mg/kg per day (P = 0.5)]. The daily polyethylene glycol requirement was less in the tramadol group for both the independent [0.5 g/kg per day *vs* 0.6 g/kg per day (P = 0.64)] and paired admissions analyses [and 0.41 g/kg per day *vs* 0.55 g/kg per day (P = 0.67)].

CONCLUSION: The addition of scheduled tramadol in patients receiving concomitant morphine and ketorolac demonstrates a trend toward decreased morphine and polyethylene glycol use.

Key words: Pediatrics; Sickle cell; Tramadol; Morphine; Vaso-occlusive crisis

Core tip: A small clinical study has shown that balanced analgesia using intravenous morphine, intravenous ketorolac, and intravenous tramadol followed by erythrocytapheresis was effective, as shown by pain relief and significant improvement in mood and sleep, in seven sickle cell disease patients aged three to twenty-eight years who presented with vaso-occlusive crisis. The objective of this study is to evaluate whether the addition of scheduled oral tramadol to intravenous morphine plus intravenous ketorolac provides adequate pain relief, and reduces morphine requirements, adverse effects, length of patient-controlled analgesia therapy, and length of hospital stay.

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INTRODUCTION

One of the major causes of hospitalization for patients with sickle cell disease (SCD) is vaso-occlusive crises (VOC). The hallmark characteristics of VOC include organ damage and pain due to the presence of dense red blood cells. The pain is generated through multiple pathways including somatic, neuropathic, and vascular mechanisms[1-4].

Balanced analgesia is a strategy based on the co-administration of drugs with different pharmacological mechanisms in order to control pain at different origins, improve the efficacy of treatment, and reduce adverse effects of each drug[5]. The administration of ketorolac and tramadol has been proven as a form of effective balanced analgesia, particularly for post-operative pain and pain caused by trauma[6]. Tramadol and its active metabolite (M1) work by binding to the mu-opioid receptors in the central nervous system (CNS) and inhibiting the reuptake of norepinephrine and serotonin, causing inhibition of the ascending pain pathway and altering the perception of and response to pain[7]. Tramadol is clinically known to have a better safety profile than the other major opioids, causing less respiratory depression and constipation.

In 2005, de Franceschi *et al*[8] published a study evaluating balanced analgesia using intravenous (*iv*) morphine, *iv* ketorolac, and *iv* tramadol followed by erythrocytapheresis in seven SCD patients aged three to twenty-eight years who presented with VOC. The co-administration of tramadol and ketorolac was effective in all VOC, as shown by pain relief and significant improvement in mood and sleep. The use of erythrocytapheresis, which is not available at our hospital, Moses Cone Memorial Hospital (MCMH), likely contributed to pain relief in this study.

At MCMH pediatric patients who presented prior to August 2010 with VOC caused by SCD were routinely prescribed *iv* morphine and *iv* ketorolac for pain control. However, because of the high morphine requirement in this patient population, severe respiratory depression and constipation can occur. After August 2010, pediatric physicians began adding scheduled oral (*po*) tramadol to the standard regimen of *iv* morphine patient-controlled analgesia (PCA) and *iv* ketorolac in an attempt to reduce narcotic-induced side effects. The objective of this retrospective study is to evaluate whether the addition of scheduled *po* tramadol to *iv* morphine and *iv* ketorolac reduces morphine requirements, provides adequate pain relief, decreases length of hospital stay, and reduces severe respiratory depression, severe constipation, and length of PCA therapy.

MATERIALS AND METHODS

This single-centered, Institutional Review Board (IRB)-approved, retrospective study included pediatric patients who were ⩾ 2 years old with VOC caused by SCD, were on PCA morphine and *iv* ketorolac and had scheduled *po* tramadol added to their regimen. Tramadol was dosed at 1-2 mg/kg per dose *po* every four to 6 h (max: 400 mg/d and 100 mg/dose) and ketorolac at 0.5 mg/kg per dose *iv* every 6 h (Max: 30 mg/dose). Morphine PCA orders included a basal rate, intermittent dose, lockout interval, and a 1-hour and 4-hour limit. Using the International Classification of Diseases (ICD)-9 code for SCD, all patients < 21 years old who were admitted between March 2008 and March 2011 were included in this retrospective review. Patients were excluded from the review if they did not have a diagnosis of VOC or did not receive morphine PCA. The data was collected from electronic records and included age, weight, morphine use, tramadol use, hemoglobin, pain scores, number of days on PCA, length of hospital stay, respiratory rate, and polyethylene glycol (PEG) use. All patients were analyzed as independent admissions. Additionally, patients with multiple admissions during the study period (at least one with morphine only and one with both morphine and tramadol) were analyzed as paired admissions, acting as their own controls.

The primary outcome of this study was average daily morphine requirement. Secondary outcomes included average pain scores, respiratory rate, PEG dose, length of PCA therapy and number of days in the hospital.

All patients were analyzed as independent admissions using the Wilcoxon Rank Sum test. Patients who had multiple admissions, one with tramadol use and one without were also analyzed as paired admissions using the Wilcoxon Signed Rank test. The statistical analysis was completed using Stata, Version 10.1 (Cary, NC).

RESULTS

Between March 2008 and March 2011 eighteen pediatric SCD patients with VOC received morphine PCA and *iv* ketorolac and twelve patients received morphine PCA plus *iv* ketorolac and scheduled *po* tramadol. Baseline characteristics were similar between both groups with the exception of the average weight, which was greater in the tramadol group than in the morphine group because the latter group had a younger sample (Table 1).

Average morphine requirements with and without tramadol were similar in the independent admission analysis [0.58 mg/kg per day and 0.65 mg/kg per day, respectively (P = 0.31)]. Average morphine requirements with and without tramadol were also similar in the paired admissions analysis [0.71 mg/kg per day and 0.77 mg/kg per day, respectively (P = 0.5)]. Contradictory to what was expected, pain scores were higher when tramadol was added to the pain regimen for both the independent admissions (6.75 *vs* 5) and the paired admissions (6.5 *vs* 5.5). The daily

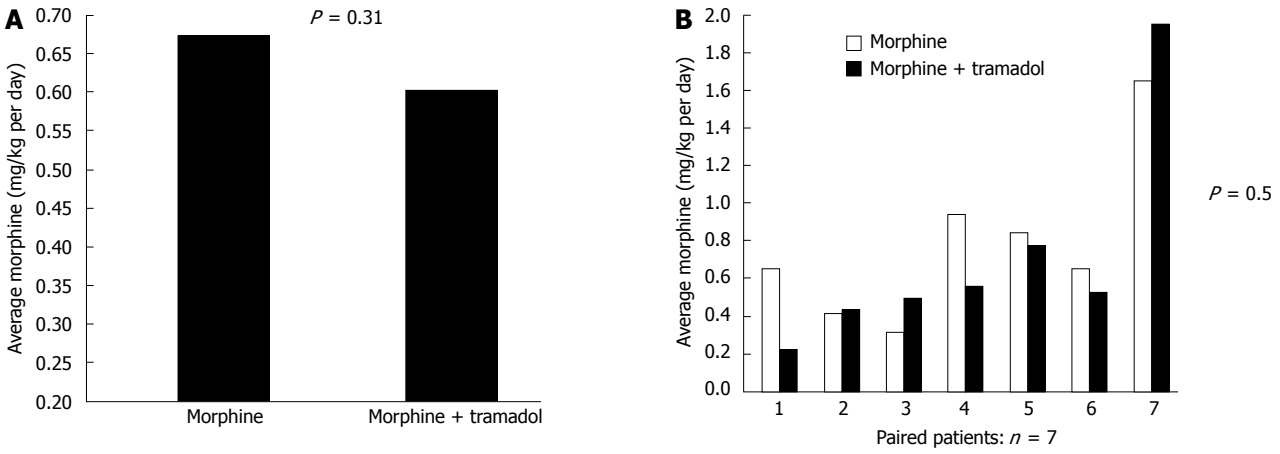

Figure 1 Average morphine requirement for independent admissions (A) and average morphine requirement for paired admissions (B).

Table 1 Baseline characteristics

	Morphine	Morphine + tramadol
Sample size	18	12
Age (yr), Mean (range)	11.5 (3-20)	13.4 (7-20)
Gender		
Male	9	6
Female	9	6
Weight (kg), mean (range)	38.7 (11.6-77.4)	52 (27.0-77.4)[a]
Hemoglobin (mg/dL), mean (range)	9.0 (6.0- 11.9)	9.4 (6.5-12.0)

[a]$P < 0.05$ *vs* morphine.

polyethylene glycol requirement was less in the tramadol group for both the independent and paired admissions analyses (0.5 g/kg per day *vs* 0.6 g/kg per day and 0.41 g/kg per day *vs* 0.55 g/kg per day, respectively) but neither difference was statistically significant ($P = 0.64$ and 0.67, respectively). The paired admissions analysis demonstrated a greater difference in PEG requirements which, while not statistically significant, may provide a more accurate comparison. Furthermore, there was no difference in the length of stay, number of days on PCA, or respiratory rate between groups in either analysis (Tables 2 and 3).

DISCUSSION

The addition of scheduled oral tramadol in patients receiving concomitant morphine and ketorolac did result in numerically lower average daily morphine requirements (Figure 1A) and polyethylene glycol use; however, differences in these endpoints were not statistically significant (Table 2). In the paired admissions analysis, four of the six patients who received less than 1 mg/kg per day of morphine used less morphine when tramadol was added to their regimen (Figure 1B); however, pain scores did not correlate with the decreased morphine requirement.

The lack of correlation between pain scores and morphine requirement may be due to the subjectivity of pain. After completion of the study, a pediatric psychiatrist spoke with several patients in the study and found that many patients did not understand how to use the visual analogue pain scale or the numeric scale to rate their pain. When asked to rate their pain as red, yellow or green (red corresponding to the most pain and green the least), patients gave more accurate representations of their true pain level. Extensive education on rating pain would be required to provide a more precise representation of pain relief with and without the use of tramadol.

There were several limitations to this study. The retrospective nature of the study forced us to rely on electronic nursing documentation for all of our data collection, which may have resulted in some inaccurately charted data. Frequently, bowel movements were not documented. We therefore measured average daily polyethylene glycol use to assess constipation. Additionally, we were unable to stratify patients based on their basal morphine PCA rate and determine how much of their daily morphine requirement was due to demand dosing, as this information was not documented electronically. Patients with multiple admissions for VOC can develop tolerance to narcotics, resulting in an increased morphine basal rate requirement. Documentation of this may have provided a more accurate assessment of which analgesic regimen provided better pain control and fewer narcotic-induced side effects.

VOC most commonly involves the back, legs, knees, arms, chest and abdomen. The location of the vaso-occlusive crisis has a significant impact on the intensity of pain and the abilitiy to control that pain; however, this study did not stratify patients based on VOC location or disease severity[9]. Additionally, the disease severity has interpatient and intrapatient variability making it more difficult to compare patients. Also, one patient in this study had drug-seeking behavior, which may have skewed the results causing increased average morphine requirement and pain scores.

A larger, controlled study would be more likely to determine statistical difference in the primary and secondary endpoints. Pediatric physicans at MCMH no longer routinely prescribe tramadol in this population but con-

Table 2 Independent admissions statistical analysis

	Morphine (n = 18)	Morphine + tramadol (n = 12)	P-value[1]
Morphine requirement (mg/kg per day), mean ± SD	0.65 ± 0.35	0.58 ± 0.48	0.31
Pain score, median (range)	5 (0-8)	6.75 (3-9)	0.07
PCA duration (d), median (range)	4.5 (0-13)	5 (3-14)	0.33
LOS (d), median (range)	7 (4-14)	7.5 (3-17)	0.85
Respiratory rate, mean (range)	21 (14-29)	19 (16-23)	0.28
Polyethylene glycol dose (gm/kg per day), mean (range)	0.6 (0-1.66)	0.5 (0-1.12)	0.64

[1]*P*-value calculated using Wilcoxon Rank Sum test. PCA: Patient-controlled analgesia; LOS: Length of stay.

Table 3 Paired admissions statistical analysis (n = 7)

	Morphine	Morphine + tramadol	P-value[1]
Morphine requirement (mg/kg per day), mean ± SD	0.77 ± 0.44	0.71 ± 0.57	0.50
Pain score, median (range)	5.5 (2-8)	6.5 (3-8)	0.27
PCA duration (d), median (range)	6 (4-13)	7 (3-10)	0.35
LOS (d), median (range)	7 (5-14)	9 (3-12)	0.61
Respiratory rate, mean (range)	19 (14-20)	19 (17-23)	0.87
Polyethylene glycol dose (gm/kg per day), mean (range)	0.55 (0.28-1.1)	0.41 (0.28-0.98)	0.67

[1]*P*-value calculated using Wilcoxon Rank Sum test. PCA: Patient-controlled analgesia; LOS: Length of stay.

tinue to use it in patients who have clinically shown improved pain control with tramadol in the past. Tramadol use is appropriate in this population as it has proven safe, usually causing no additional side effects and potentially providing some benefit in controlling pain and reducing narcotic-induced constipation. If tramadol continues to be clinically beneficial for pain control in other patients in this population, it may be possible to review our primary and secondary endpoints on a larger scale to determine any true differences.

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COMMENTS

Background

Pain is a hallmark of vaso-occlusive crisis (VOC) caused by sickle-cell disease (SCD). Intravenous (*iv*) morphine plus *iv* ketorolac is generally the combination of choice for VOC in SCD patients at Moses Cone Memorial Hospital (MCMH); however, morphine can cause severe respiratory depression and constipation. The objective of this study is to evaluate whether the addition of scheduled oral tramadol to *iv* morphine plus *iv* ketorolac provides adequate pain relief, and reduces morphine requirements, adverse effects, length of PCA therapy, and length of hospital stay.

Research frontiers

In 2005, de Franceschi *et al* published a study evaluating balanced analgesia using *iv* morphine, *iv* ketorolac, and *iv* tramadol followed by erythrocytapheresis in seven SCD patients aged three to twenty-eight who presented with VOC. The co-administration of tramadol and ketorolac was effective in all VOC, as shown by pain relief and significant improvement in mood and sleep.

Innovations and breakthroughs

This is the first article evaluating the use of oral tramadol in addition to *iv* morphine and ketorolac on whether this combination provides adequate pain relief, and reduces morphine requirements, adverse effects, length of PCA therapy, and length of hospital stay.

Applications

The study results suggest that the addition of scheduled oral tramadol in patients receiving concomitant morphine and ketorolac demonstrates a trend toward decreased morphine and polyethylene glycol use.

Terminology

Erythrocytapheresis is a process in which red blood cells are extracted from the whole blood.

Peer review

This is a very good clinical study in which the authors analyzed the efficacy of adding oral tramadol to usual pain regimen used for sickle cell pain crisis.

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