LETTER TO THE EDITOR

Chronic opioid use in patients with sickle cell disease

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Pain is the most common symptom in sickle cell disease (SCD) patients [1]. In the acute setting, SCD patients may have painful crises that require hospitalization [2]. However, these patients also suffer chronic pain, the etiology of which is not fully understood [3].

Opioids remain the mainstay of management for both acute and chronic pain in SCD patients despite risks of physical dependence, withdrawal, tolerance, and possible overdose and death [4,5]. Chronic opioid use also alters intestinal microbial community [6] and leads to increased risks for the development of Clostridioides difficile infection [7]. Despite potential adverse outcomes in chronic opioid use and specific limitations in SCD patients, there are no clear guidelines for the management of chronic pain in SCD patients. In this study, we sought to determine the risks for and clinical characteristics associated with chronic opioid use to identify the at-risk patients so that they may be offered early interventions to avert these complications.

Following approval from the Institutional Review Board, data from 449 patients were collected. There were 258 females and 191 males; 98% were Black/African-American. Their median age was 39 years (range 3–88). Their phenotypes were HbSS (284/449) (63%), HbSC (101/449) (22.5%), HbSβthal (54/449) (12%), and unknown or others (10/449). The prevalence rate of chronic opioid use (with 95% CI) is shown in Figure 1. Not surprisingly, the risks increase steadily from age 20 years to 55 years.

We next examined the clinical factors associated with chronic opioid use among those age 18 and over (Table 1). In univariate analysis, we identified that chronic opioid users are more likely to be female (p < 0.0001) and have higher baseline total white cell count (median $10 \times 10^9$/L vs $9 \times 10^9$/L) (p = 0.0009), non-HbSC phenotype (p = 0.034), been prescribed hydroxyurea (p = 0.000047), and concurrent psychiatric illness (p = 0.018). Lower hemoglobin (8.5 g/dL vs 8.9 g/dL) (p = 0.055) and presence of chronic arthritis (p = 0.06) trend towards significance for chronic opioid use. Multivariate analysis found that patients with higher total white cell count (p = 0.0007), psychiatric illness (p = 0.0059), and users of hydroxyurea (p = 0.0001) were particularly at risk. Patients with a total white cell count of $15 \times 10^9$/dL or above were 2.2 (95% CI: 1.45–3.37) times more at risk (p = 0.0024) for chronic opioid use than those whose total white cell counts were below $15 \times 10^9$/dL.

In this study, we have identified a group of adult sickle cell patients who are at risk for chronic opioid use. The data from our univariate analysis suggests that, in addition to concurrent psychiatric illness, patients with more severe disease are at higher risks for chronic opioid use. These patients tend to have...
higher total white cell counts, be more anemic, have chronic arthritis, and be more likely to have been prescribed hydroxyurea. The association between chronic opioid use and higher total baseline white cell count is consistent with data showing that this is also the same group of patients who are at higher risks for strokes [8] and early death [9]. This association may reflect elevated levels of baseline systemic inflammation and its contribution to chronic pain. Not unlike adult patients in the general population [10], SCD patients with mental health disorders are significantly more at risk for chronic opioid use than those without mental health disorders.

In conclusion, chronic opioid use is prevalent among adult SCD patients. The identification of the clinical characteristics that are associated with the development of chronic opioid use provides the framework for healthcare providers to recognize these patients early and be proactive in their intervention. The chronic use of opioids most likely reflects the lack of mechanistic management of pain. For these at-risk patients, a multidisciplinary approach early in their disease course may be beneficial. The approach may include the implementation of non-opioid pain management methods such as the use of cannabinoids and intranasal ketamine, and early orthopedic intervention in those with chronic arthritis and avascular necrosis to curtail the duration of use of opioid analgesia. Psychosocial support and patient/family education should also be offered at the onset of the use of opioid analgesia in the outpatient setting.

Disclosure statement
No potential conflict of interest was reported by the author(s).

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