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HIGHLIGHT

Still seeking balance in opioid management for acute sickle cell disease pain

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Management of severe vaso-occlusive pain episodes (VOEs), the hallmark symptom of sickle cell disease (SCD), remains a deep-rooted challenge. VOEs, often referred to as "crises" by those living with SCD, increase in frequency through adolescence and adulthood, often disrupting education, work, and family life.[1] Compounding the unpredictability of VOEs is the lack of targeted therapies for acute vaso-occlusion.[2] Hence, opioids have been the mainstay of SCD pain management along with nonsteroidal anti-inflammatory drugs (NSAIDs) and nonpharmacological care such as warm compresses and distraction strategies. To facilitate self-management during hospitalization for VOE, intravenous opioids are often prescribed as patient-controlled analgesia (PCA) with continuous infusion and demand dose available.[3] While opioids are needed for acute VOE management, repeated or prolonged treatment with opioids can lead to tolerance (in which a given dose of medication no longer produces the same beneficial effect), physical dependence (in which the drug's presence is required for normal physiological function), and opioid-induced hyperalgesia (in which pain experience is amplified due to sensitization of nociceptive pathways).[4] Furthermore, individuals with SCD may have pain due to non-VOE causes, such as neuropathic pain, migraine, or muscular pain, which are difficult to distinguish from VOEs and may be worsened by opioid exposure. Despite the increase in prevalence of opioid use disorder in the United States, its prevalence in people with SCD appears to remain low, but fear of opioid use disorder has had negative consequences for those with SCD.[5] There is no standard opioid management strategy for VOE; opioid doses are typically prescribed based on physician discretion, pain severity, and institutional common practice. It would be ideal, therefore, to identify VOE management options that improve pain management while reducing the potential negative effects of opioids.

In this issue of *Pediatric Blood and Cancer*, Carullo and colleagues have described their center's retrospective experience with a novel VOE management clinical practice guideline (CPG).[6] Before their CPG implementation, individuals with VOE received PCA with continuous infusion opioids plus patient-controlled bolus opioid doses. The novel CPG involved reliance on bolus dosing only, with the option to prescribe oral methadone, a long-acting mu-opioid receptor agonist and N-methyl-D-aspartic acid receptor (NMDA) antagonist, for patients whose pain did not improve rapidly. NSAIDs were included in both time periods. While the CPG was implemented for all children and young adults hospitalized with SCD at their institution, the published analysis was restricted to patients aged 5–21 years with three to eight admissions for pain per year. The authors report a shorter duration of hospitalization, decreased opioid exposure, and fewer episodes of acute chest syndrome during admissions using the new CPG. Pain scores improved more rapidly during admissions using the bolus-only strategy. Notably, the 30-day readmission rate was high in both groups but did not increase with the change in pain management strategy.

These results are promising, yet there are several unresolved questions about this VOE management strategy, as the authors acknowledge. First, both cohorts consisted of a small number of frequently admitted individuals: 17 patients with 73 admissions preimplementation and 19 patients with 72 admissions postimplementation. While the guideline is intended for ages 5 years and older, among the analyzed individuals, the mean age at admission was 15–16 years in both time periods. Adolescents with three or more VOE admissions per year represent a small fraction of those living with SCD, so the impact of this pain management strategy for patients with less frequent pain admissions, or those who have more severe pain on admission, is not clear. Second, in this retrospective study, patients'

satisfaction with this opioid-sparing strategy was not ascertained. Without a continuous opioid, was their sleep disrupted so they could receive patient-controlled bolus opioids throughout the night? Was pain control adequate to permit ambulation and participation in self-care tasks like bathing and in physical or child life therapies during hospitalization? These questions should be addressed prospectively before this strategy can be endorsed for all pediatric SCD VOE admissions.

Ideally, management of pain in SCD would incorporate more targeted treatments in addition to reduced exposure to opioids. This approach may facilitate better pain control while limiting the negative effects of opioids including physical dependence, hyperalgesia, and development of opioid use disorder. In 2014, the NHLBI published the first consensus guidelines that addressed opioid-based pain management in SCD; however, nonopioid options were minimally discussed.[3] The American Society of Hematology SCD guidelines expanded on comprehensive strategies for both acute and chronic pain while also acknowledging the paucity of evidence.[7] Recent work has shown promise targeting nociception with lidocaine and central sensitization with ketamine.[8] Working with pain management teams who can provide regional anesthesia such as nerve blocks may improve analgesia while limiting systemic opioid exposure.[9] The search for agents that may speed resolution of vaso-occlusion continues, with a current NHLBI-funded trial Sickle Cell Disease Treatment with Arginine Therapy (STArT) Trial (NCT # NCT04839354). Nonpharmacological pain management strategies, such as virtual reality and cognitive-behavioral therapies, have shown promise in reducing pain experiences and should be incorporated in multidisciplinary pain management plans.[10] Pain prevention should be prioritized by expanding the use of hydroxyurea and other new agents shown to reduce pain frequency in those with SCD.[2] Clinical trials with the endpoint of pain prevention have been far more successful than trials that focus on pain treatment in SCD, and reducing the frequency and severity of acute pain may be the key to preventing the chronic pain that many adults with SCD experience.[2]

Importantly, Dr. Carullo and colleagues have described successful opioid use reduction in a high-risk subset of the SCD population: adolescents with intermediate to high hospital utilization. In these patients, lower opioid exposure may reduce the risk of developing opioid-induced hyperalgesia, chronic pain, physical dependence, and even opioid use disorder. When considering the greater population, though, the benefits of reducing opioid exposure should not eclipse the goal of alleviating the suffering of acute pain. And for all individuals with SCD, pain management should be paired with increasing access to preventive therapy and even curative therapy to finally eliminate the physical, social, and emotional pain of VOEs.

CONFLICT OF INTEREST

TAF: Consulting: Novartis, Forma Therapeutics, Global Blood Therapeutics, and Emmaus Medical, Inc. MLH: Consulting: Bluebird Bio; research funding: Forma Therapeutics, Global Blood Therapeutics; spouse employment: Pfizer, Inc.

LINKED ARTICLE

This article is linked to an article by Veronica Carullo et al. https://onlinelibrary.wiley.com/doi/epdf/10.1002/pbc.29665

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