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EDITORIAL

One Small Step for Sickle Cell Disease: Many More to Go

Sickle cell disease (SCD), the most commonly inherited blood disorder in the United States, primarily affects a minority population and has been chronically underfunded. Despite its claim to fame as the "first molecular disease identified," SCD has not been given sufficient attention, advocacy, or empathy (1). Until recently (2018), the only medication approved by the U.S. Food and Drug Administration for SCD was hydroxyurea, a chemotherapeutic that was accidentally noted to benefit persons with SCD through fetal hemoglobin induction, leukoreduction, and nitric oxide donation (2). Although useful in the reduction of acute painful events, hydroxyurea (and other new agents, including L-glutamine, crizanlizumab, and voxelotor) incompletely modifies outcomes in SCD (3). Acute painful events, known as sickle cell crisis or vaso-occlusive crisis (VOC), are the hallmark feature of a highly complicated disease. At present, no medications functionally reduce a VOC event once it has begun. Instead, opioid medications are the only option to reduce the pain caused by microvascular injury (although they do not reduce the damage underlying the pain, and their side effects and risk profile are at great expense). However, quick and effective reduction of pain can allow patients to more easily move, stretch, and breathe—important to increase oxygenation and restore blood flow, which will eventually abate the crisis. Thus, aggressive management of VOC may lead to a shorter duration of pain (4). As a result, guidelines written by both the National Institutes of Health and the American Society of Hematology prioritize the appropriate and rapid management of VOC (5).

In their study, Lanzkron and colleagues (6) sought to show the improved effectiveness of a specialized infusion center (IC) over the emergency department (ED) for the treatment of acute VOC in SCD. The ED has historically been the location for treatment of acute VOC. However, it is often overburdened and may not be the optimal place for acute care if another option exists. In the case of SCD, the ED is also a place of fear and mistrust between provider and patient—as well as patient and provider—increasing the difficulty of achieving satisfactory results. Further, because the ED is often overwhelmed with trauma, stroke, and cardiac arrest, patients with SCD reporting pain (usually severe and excruciating) are often deprioritized or overlooked. Specialized ICs have been created to improve outcomes in the management of acute VOC. The ESCAPED (Examining Sickle Cell Acute Pain in the Emergency Versus Day Hospital) study was designed to evaluate the outcomes of a specialized IC compared with the ED in a multicenter setting.

The study methodology is remarkable for several reasons. First, a substantial number of patients were enrolled and followed continuously for 18 months in which both subjective and objective data were obtained. Second, sufficient data were available such that no outcome data were imputed. Third, pain is nebulous and hard to quantitate in all studies (a primary reason why SCD has had so few successes); this increases the difficulty of comparing outcomes involving pain in different locations. To avoid comparing pain scores, this study used more quantifiable outcomes (such as time to first intravenous opioid and frequency of admissions).

The ESCAPED study used a pragmatic, prospective design to compare outcomes between a specialized IC and an ED for the treatment of SCD VOC. The study was done in 4 geographically distinct U.S. cities that each have a specialized IC and an ED within the same hospital. To avoid the complication of obtaining consent from a person in severe pain (whose judgment may be impaired by medication), individuals gave consent at their regular, nonacute, outpatient appointment and then were assessed monthly for acute events. To ensure the most robust data collection possible, both patient reports and state-level data exchange programs were used to assess for acute care visits.

ESCAPED clearly showed the improved management of SCD-related acute pain in ICs compared with EDs. The time to first dose of intravenous opioids was twice as long in the ED, and the chance of being admitted (for insufficiently treated pain) was 4 times as great. The study also showed that an ED is not needed for uncomplicated VOC treatment and may not be optimal. The sites chosen for this study also deserve recognition: They were geographically distinct and included both academic and community-based hospitals with different models of staffing and care. Thus, a large academic SCD center is not required to achieve improved outcomes. Instead, the results show both the importance of access to an SCD specialist and the benefits of a specialized IC for optimal treatment.

In addition to the obvious findings above, there are several other important take-home points. All of the patients in this study were adults with SCD who were fortunate enough to be in the care of an SCD specialist. Although this may not surprise providers who routinely treat persons afflicted by cancer or cystic fibrosis, there is a paucity of adult-focused SCD specialists in the United States. Recent data suggest that fewer than 30% of affected adults are seeing a specialist who can initiate an individualized pain plan or recommend disease-modifying therapy. Instead, many patients with SCD are treated by a primary care physician or primary oncologist without sufficient SCD expertise. In addition, because there is no national funding for SCD centers, few exist. A recent study was done to identify the requirements of a sickle cell center, and now further work is ongoing to define and assess quality metrics (7). Compared with other conditions, SCD is very behind.

It is also important to reflect on cost savings with the use of IC models. The IC model results in decreased hospital admissions and, subsequently, decreased hospital-related morbidity and cost of care. The cost savings are to the payer and the affected individual—not the hospital system. The hospital may understand the value of these savings only if a more "profitable" patient is placed in the now-unoccupied hospital bed, or in terms of cost

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avoidance. Although value-based health care is the goal of improving the patient care experience and population health with reduced cost, the hospital system's understanding of this value remains controversial (8).

Finally, the recent pandemic has revealed the ugly underbelly of the American health care system, in which not all individuals have appropriate access to care or health care coverage. Sadly, these individuals are most often people of color who are also negatively affected by numerous other social determinants of health. Providers specializing in SCD have always recognized these bitter truths in the health care system and are constantly fighting for ethical, equitable care for our patients. The value in the IC model must be recognized as important because the model offers a better way to manage this horrific disease. It is equally important that the IC model is recognized as valuable to the hospital system—or as a requirement to do what is right for those living with SCD.

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