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Pain without gain: steroids and sickle crisis

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In this issue of *Blood*, Walter et al[1] report on the association of corticosteroid exposure and subsequent hospitalization for vaso-occlusive episodes (VOEs) in people with sickle cell disease (SCD).

In theory, corticosteroids are an appealing treatment for severe SCD complications because they are inexpensive, are readily available, and have strong anti-inflammatory effects. However, evidence suggests that, in practice, the benefits may not outweigh the risks. Limited evidence highlights the concern: a randomized controlled trial of dexamethasone for acute chest syndrome in children with SCD reduced the need for blood transfusions, the duration of fever, and the need for oxygen and analgesic therapy.[2] However, rehospitalization occurred within 72 hours in 27% of children treated with dexamethasone compared with only 4.7% of children treated with placebo. A study of methylprednisolone to treat VOEs in children reported similar outcomes.[3] Subsequent retrospective studies and case series report an association of corticosteroid exposure with VOEs and even stroke.[4,5] A recent meta-analysis by Lopinto et al[6] that estimated the effect of corticosteroids on the clinical course of VOEs or acute chest syndrome included 6 studies (3 randomized controlled studies and 3 retrospective studies) and concluded that compared with standard treatment, corticosteroids were associated with an increased risk of hospital readmission.

Corticosteroid exposure for individuals with SCD is not limited to treating SCD complications. Corticosteroids are prescribed for myriad acute conditions ranging from bee stings and asthma to optic neuritis. Periprocedural exposure in which dexamethasone may be used as an antiemetic also occurs.[7] Prescribing physicians may be aware of the many established adverse effects of steroids such as immunosuppression, leukocytosis, hypertension, fluid retention, osteonecrosis, sleep disruption, and psychosis, but they often lack knowledge specific to SCD about the potential risks with steroid treatment for this patient population. In our experience, well-meaning clinicians prescribe corticosteroids for seemingly reasonable indications. This comes to our attention when those treatments precipitate what are often very severe VOEs. Neither the clinician nor the patient are aware of the risks associated with corticosteroid exposure in this population, likely because of the limited literature describing this phenomenon.

In this setting, Walter et al applied a rigorous, somewhat novel method to analyze real-world data about corticosteroid exposure and association with hospitalization for VOEs. The authors use a case-case time control design in a nationwide population-based cohort from the French national health insurance database. To adjust for temporal variations in the exposure, the authors used an adjusted control cohort in which the probability of exposure was similar to that for patients. They matched this cohort of future patients by using demographic characteristics, which resulted in 5151 patients for analysis. They excluded exposure to topical or inhaled corticosteroids and examined prescriptions of systemic corticosteroids as a proxy for patient exposure. During the study period, a remarkable 45% of patients were exposed at least once to systemic corticosteroids. The median time between dispensing of corticosteroids and hospital admission was 5 days. Corticosteroid exposure was associated with an increased risk of hospitalization for VOEs (adjusted odds ratio, 2.6; 95% confidence interval, 1.1-6.4), this risk of admission was lower in those prescribed hydroxyurea, in men, and in children.

The mechanistic explanation for corticosteroid association with VOEs is not well defined, but likely involves the interaction of established corticosteroid mechanisms with SCD inflammatory, hemolytic, and vasculopathic mechanisms.

Walter et al add important data about the association of corticosteroid use with subsequent VOEs. In so doing, they have contributed meaningfully to a growing body of evidence that suggests extreme caution is warranted when prescribing systemic corticosteroids to individuals with SCD. For circumstances in which corticosteroids are absolutely indicated, involving a provider with SCD expertise is essential. This study highlights several directions for future research. More data are needed to define whether causal and potentially targetable mechanisms explain the association described, to understand the sex difference identified here, and to define the use of prophylactic transfusion to mitigate corticosteroid-associated VOEs.[8] Transfusion may be valuable when there are no reasonable alternatives to corticosteroids.

Attending to corticosteroid use in individuals with SCD is tied to larger trends in corticosteroid prescribing. Dexamethasone is emerging as a treatment standard for patients with hypoxia associated with COVID infection. This reality highlights the pressing need for more information about corticosteroid treatment in individuals with SCD during acute illness. In addition, there is growing recognition that corticosteroids are overprescribed. A striking percentage of study patients were exposed to systemic corticosteroids in this study. In the United States, a study of 1.5 million adults enrolled in a health insurance plan for 2 years found that 21% of patients were prescribed a short course

of systemic corticosteroids.[9] For many indications, prescribing corticosteroids leads to an increase in harm without benefit.[10] The risk of VOEs and hospital readmission in individuals with SCD should be added to the list of potential harms.

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