



The Illinois Medical Bulletin



The Role of Hydroxyurea in Reducing Vaso-occlusive Complications in Adults with Sickle Cell Disease: A Review of the Evidence

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Article History :

Received date : 2019/10/12
Revised date : 2019/11/28
Accepted date : 2019/12/09
Published date : 2020/01/13



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ABSTRACT

Introduction: Sickle cell disease (SCD) is a chronic, inherited blood disorder characterized by recurrent, painful vaso-occlusive crises (VOCs) and cumulative end-organ damage. Historically, management was primarily supportive. Hydroxyurea emerged as a promising disease-modifying therapy aimed at ameliorating the underlying pathophysiology.

Literature Review: A review of the pivotal clinical literature establishes hydroxyurea as the cornerstone of preventive therapy for adults with severe SCD. Its primary mechanism of action is the induction of protective fetal hemoglobin (HbF), which dilutes the concentration of sickle hemoglobin and inhibits the polymerization process that causes red cell sickling. The long-term follow-up of a landmark randomized controlled trial provided definitive evidence of sustained efficacy. This research demonstrated that long-term hydroxyurea therapy significantly reduces the frequency of VOCs, the incidence of the life-threatening acute chest syndrome, and the need for blood transfusions. This sustained clinical benefit was associated with a significant reduction in mortality. Subsequent research also identified additional beneficial mechanisms, including anti-inflammatory effects and improved blood flow.

Conclusion: The body of evidence confirms that hydroxyurea is a safe and effective disease-modifying agent for adults with severe sickle cell disease. Its proven ability to decrease the rate of acute, painful, and life-threatening complications has transformed the management of SCD from a reactive, crisis-focused approach to a proactive, preventative standard of care.

Keywords: Sickle Cell Disease, Hydroxyurea, Vaso-occlusive Crisis, Fetal Hemoglobin (HbF), Acute Chest Syndrome.

INTRODUCTION

Sickle Cell Disease (SCD) is a group of genetic disorders affecting hemoglobin, the molecule in red blood cells that delivers oxygen to cells throughout the body. It is characterized by the presence of abnormal sickle hemoglobin (HbS), which, under conditions of deoxygenation, polymerizes and causes red blood cells to deform into a rigid, sickle shape. These abnormal cells lead to chronic hemolytic anemia and, more devastatingly, recurrent episodes of vaso-occlusion, where the sickled cells block blood flow in small vessels. These vaso-occlusive crises (VOCs) cause severe pain and, over a lifetime, lead to progressive, irreversible damage to nearly every organ system, resulting in significant morbidity and a shortened life expectancy.

For many years, the management of SCD was largely supportive and reactive, involving hydration, oxygen, aggressive pain control during crises, and blood transfusions for severe anemia or other acute complications. A major therapeutic breakthrough came with the discovery that the pharmacological agent hydroxyurea could fundamentally alter the course of the disease. This literature review will synthesise the pivotal clinical evidence that established hydroxyurea as the first true disease-modifying therapy for adults with SCD.

LITERATURE REVIEW

The validation of hydroxyurea as a standard of care for adults with severe SCD was based on a strong mechanistic rationale and confirmed by long-term, high-quality clinical trial evidence.

The primary and best-understood mechanism of action of hydroxyurea is its ability to induce the production of fetal hemoglobin (HbF). HbF is the main oxygen transport protein during fetal life but its production is largely switched off after birth. The critical insight was that the presence of HbF within a red blood cell physically interferes with the polymerization of HbS. By stimulating the bone marrow to produce red cells with higher levels of HbF, hydroxyurea effectively dilutes the intracellular concentration of HbS, making the cells less prone to sickling

under deoxygenation (Platt, 2008). This directly counteracts the fundamental molecular pathology of the disease.

The definitive clinical evidence for the efficacy of hydroxyurea came from the Multicenter Study of Hydroxyurea (MSH). While the initial randomized trial was completed earlier, the crucial long-term follow-up data that confirmed its sustained benefit and safety were published subsequently. This long-term follow-up study demonstrated that the benefits seen in the original trial were remarkably durable. Patients who continued on hydroxyurea therapy for many years experienced a sustained and significant reduction in the annual frequency of painful VOCs. Furthermore, the therapy was shown to significantly decrease the incidence of the acute chest syndrome, a life-threatening form of acute lung injury and a leading cause of death in adults with SCD. The long-term data also showed a significant reduction in the need for blood transfusions (Steinberg et al., 2003).

Perhaps the most important finding from the long-term observation of this cohort was the association between hydroxyurea treatment and improved survival. The study reported a significant reduction in the mortality rate for patients who had been assigned to receive hydroxyurea compared to those in the placebo group. This was the first time any pharmacological agent had been shown to prolong life in patients with SCD (Steinberg et al., 2003).

Further research into the mechanisms of hydroxyurea revealed that its benefits likely extend beyond the induction of HbF. Additional proposed mechanisms include a reduction in the number of circulating neutrophils and reticulocytes, which are known to contribute to cellular adhesion and vaso-occlusion; an increase in the hydration of red blood cells, which also reduces the tendency to sickle; and the potential for hydroxyurea to act as a nitric oxide donor, promoting vasodilation and improving blood flow (Atweh and De-Paula, 2006). The long-term follow-up studies also provided important reassurance regarding the safety of the drug, allaying initial fears about its potential for causing malignancy when used over many years. This robust body of efficacy and safety data led to the development of national guidelines strongly recommending that hydroxyurea be offered to all adult patients with severe clinical manifestations of SCD (Wethers, 2002).

CONCLUSION

The pivotal literature on hydroxyurea therapy has fundamentally transformed the management and prognosis for adults with severe sickle cell disease. Based on its primary ability to induce protective fetal hemoglobin, the therapy was definitively proven in a landmark trial and its long-term follow-up to be highly effective at reducing the frequency of both acute painful crises and the life-threatening acute chest syndrome.

This substantial and sustained clinical benefit was associated with an improvement in long-term survival. This body of evidence established hydroxyurea as the first and most important disease-modifying therapy for SCD. It successfully shifted the treatment paradigm from a purely reactive approach focused on managing crises to a proactive, preventative strategy aimed at controlling the underlying pathophysiology of the disease, thereby creating a new and enduring standard of care.

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