

A breath of relief: nitrous oxide in sickle cell disease

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This issue of *Haematologica* features a promising preclinical study by Oddo *et al.*¹ on HBI-201, an innovative oral formulation of nitrous oxide (N₂O), intended to prevent vaso-occlusive pain in sickle cell disease (SCD). The authors show that HBI-201 effectively mitigates acute pain and hyperalgesia induced by cold exposure in a mouse model of SCD, while avoiding the side effects typically associated with inhaled N₂O and opioid analgesics. This study highlights a long-standing but underappreciated clinical challenge: finding better ways to manage pain in SCD.

Pain is the hallmark of SCD, with acute vaso-occlusive crises (VOC) being the most frequent cause of emergency visits and hospitalizations.^{2,3} Despite years of research, pain management remains largely dependent on non-steroidal anti-inflammatory drugs (NSAID) and opioids. Unfortunately, these treatments are often insufficient to fully manage pain in SCD and are related to significant side effects, including tolerance, sedation, and dependence.^{2,4} This therapeutic gap reinforces the urgent need for new pain management strategies that are both effective and safe, tailored to the unique pathophysiology of SCD pain.

Recent progress in basic and preclinical research has significantly advanced our knowledge on the mechanisms driving hyperalgesia and pain in SCD. In particular, studies using transgenic mouse models of SCD have demonstrated that cold exposure, a known trigger of VOC, induces robust mechanical and heat hyperalgesia as well as characteristic pain-related behaviors,^{5,6} closely resembling the spontaneous pain episodes reported by patients hospitalized for VOC. Moreover, recent evidence highlights the role of inflammatory pathways, complement activation, and neuroimmune interactions in the amplification of nociceptive signaling in SCD, providing a promising landscape for potential therapeutic targets.^{5,7}

The authors make significant progress in this field by assessing HBI-201 efficacy. This innovative oral formulation delivers low levels of N₂O, significantly lower than those achieved with inhaled N₂O, and therefore decreases the chance of systemic side effects. Their data show that HBI-

201 reverses mechanical and thermal hyperalgesia induced by cold exposure in SCD mice, effectively restoring pain thresholds. Importantly, the compound also attenuates spontaneous nocifensive behaviors, an important marker of ongoing pain that is often neglected in traditional pain management. Unlike morphine, HBI-201 did not induce conditioned place preference in behavioral studies, suggesting a low risk of addiction potential.⁸

These findings are consistent with previous clinical observations showing that inhaled N₂O can offer effective pain relief for acute VOC. Its use, however, has been limited by concerns about dose control, potential neurotoxicity and the risk of substance use disorder.⁹ The PHEDRE study highlighted the potential risk for misuse of inhaled N₂O among patients with SCD in France, pointing out the need for safer delivery methods that maintain analgesic efficacy while mitigating risk.⁸ The formulation of HBI-201 as an oral agent addresses many of these limitations, offering a more controlled, accessible, and convenient approach for patients.

This work might provide immediate implications in a time where the broader field of pain management in SCD has seen, finally, encouraging developments. Innovative approaches targeting ion channels, complement pathways, and neuroimmune interactions have shown promise in preclinical models, with some agents demonstrating the ability to reduce both hyperalgesia and spontaneous pain.^{5,7,10} Cannabinoids, for example, have emerged as non-opioid analgesics that can modulate pain signaling with fewer side effects compared to traditional opioids.^{11,12} While these strategies remain largely in the experimental stage, they represent a critical step toward diversifying the therapeutic strategies against SCD pain.

It is becoming more and more evident that pain in SCD is not just a symptom to be treated but a more complex pathophysiological process closely tied to disease progression, chronic inflammation and vascular dysfunction.^{4,5} Effective pain management, therefore, has the potential to not only to improve quality of life but also to reduce

downstream complications associated with chronic pain and opioid use.^{2,3}

This work highlights the feasibility of translating mechanistic insights into meaningful therapeutic advances. HBI-201's ability to block hyperalgesia in preclinical models without causing tolerance or sedation is particularly promising and therefore justifies further clinical evaluation. Additional studies should explore its potential effects on VOC frequency, hospitalization rates, opioid consumption, and most importantly, long-term safety.

In conclusion, it is time to bring pain management to the frontline of research and care in SCD. The encouraging results from this study should motivate renewed efforts to develop therapies that are safe, effective and accessible

world-wide; and specially new therapies that address the complex nature of pain in SCD. By fostering collaboration among researchers, clinicians, industrial partners and patients, we can accelerate the translation of basic research into practical solutions that make a meaningful difference in the lives of those living with this challenging disease.

Disclosures

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