EDITORIAL

Role of antioxidant therapy for pain relief in chronic pancreatitis: Finding the signal in the noise

The hallmarks of chronic pancreatitis (CP) are pain and exocrine and endocrine insufficiency. While pancreatic insufficiency is effectively managed by pharmacologic intervention, the pain associated with CP is difficult to control, often debilitating, and is a cause of major agony. This leads on to poor quality of life. The pathogenesis of pain is complex, including structural problems (obstruction by ductal strictures and stones, leading to ductal and parenchymal hypertension), inflammation, visceral hypersensitivity (neuropathic pain), and centralization of pain, leading to chronic pain syndrome. As a combination of these factors may coexist in patients with CP, no single measure may be effective. Often, this requires a multimodal approach to manage pain. The current modalities for pain management in CP include pharmacologic, behavioral, and invasive therapies, with each having varying degrees of efficacy. While the invasive modalities (endoscopic, extracorporeal shock wave lithotripsy, and surgery) may be helpful in managing pain secondary to structural abnormalities, they are only indicated in limited patients. On the other hand, to address the pain due to inflammation or neuropathic involvement, few pharmacologic therapies are reported to be efficacious and are required in almost all patients.

The initiation of pharmacologic therapy depends on the severity of pain caused by CP. The preferred first-line therapy are nonopioids analgesics [acetaminophen and Non-steroidal Anti-inflammatory Drugs (NSAIDs)], with escalation to weak opioids (tramadol and codeine) and then strong opioids (morphine, oxycodone, and fentanyl). The introduction of strong opioids typically complicates the clinical picture in these patients due to problems with dependency, tolerance, and its safety profile. Neuropathic pain secondary to visceral hypersensitivity or progressing to chronic pain syndrome may benefit from other coanalgesics such as tricyclic antidepressants, gabapentin, pregabalin, and selective serotonin-reuptake inhibitors. These therapies have been used either alone or in combination with opioid and nonopioid analgesics with variable results. Other medical therapies for pain include pancreatic enzyme replacement therapy, octreotide, montelukast, and allopurinol; however, randomized controlled trials have shown that they are not very effective in the treatment of CP-related pain.

Although all these pharmacologic interventions are the cornerstone of pain management in CP, these medications are only supportive therapies aimed at treating the concurrent symptoms and not the underlying factors in pain causation. Hence, it is important to identify targeted therapies that would address the underlying biology of pain and alter the natural history of its progression in CP. One such targeted therapy that has shown some promise in the past is antioxidant therapy (AOT).

The hypothesis for the use of AOT in pain management and to halt the progression of CP is plausible. Oxidative stress caused by short-lived intracellular reactive oxygen and nitrogen-free radicals is a common feature in all forms of CP and results in the oxidation of lipids in the cell membrane and proteins, as well as mitochondrial depolarization and DNA fragmentation.

Several experimental and clinical studies have shown increased oxidant stress and dietary insufficiency of antioxidants along with reduced antioxidant capacity in CP. Based on these findings, exogenous supplementation with antioxidants has been examined as a potential therapy for CP in the hope that it might reduce the pain. However, clinical trials and prior meta-analyses evaluating the benefits of AOT in the management of CP pain have demonstrated conflicting results, and till date, there is a lack of consensus on its efficacy for use as a standard therapy.

Today, for clinicians, the pressing issue is whether to use AOT as a pain management modality for CP. In the current issue of JGH Open, a timely analysis by Mohta et al. may help provide some clarity to guide clinicians on this issue. Mohta et al. report the results of the meta-analysis and review investigations of the effectiveness of AOT in the management of CP pain. The authors systematically reviewed PubMed and Embase databases to identity all articles published until February 2020. Based on a stringent study inclusion criterion, 12 articles were included for systematic review, of which 4 were included for meta-analysis. The authors report that, compared to the placebo arm, the antioxidant arm did not show a significant reduction in CP pain (either by visual analog scale or pain-free participants), increase in adverse events, or any effect on quality of life. They also noted no difference in the outcome based on different etiology of CP or by age groups. Based on their findings, the authors conclude that AOT is not beneficial in pain management for CP, and its routine use should be reconsidered.

Prior to this, all other meta-analyses conducted to determine the efficacy of AOT have demonstrated some benefit in CP pain management. The first meta-analysis by Rustagi and Njei showed a 27% decrease in pain-free participants along with a reduction in narcotic usage, concluding that AOT is clinically beneficial to use. Subsequently, similar meta-analysis and reviews by Cai et al., Talukdar et al., and Zhou et al. reported concurrent findings, where a statistical benefit of using AOT for CP pain management was demonstrated. However, it is important to note that the majority of patients included in these meta-analyses are mainly contributed by two large studies conducted in 2009 and 2012: Bhardwaj et al. (2009), reporting beneficial effects of AOT in pain management of CP (n = 147), and Siriwardena et al. (2012), reporting failure of AOT for pain management in CP (n = 92). Despite conflicting results from these
two major studies, most of the reports from aforementioned studies have been able to demonstrate a marginal beneficial effect, suggesting a potential therapeutic advantage for its use.

Since the last meta-analysis, the literature on AOT efficacy in CP pain has been updated. Singh et al. conducted a double-blind randomized placebo-controlled trial with 107 patients and found no significant reduction in pain in patients with CP on antioxidants compared to the placebo group.10 Interestingly, after inclusion of the trial by Singh et al., in the current meta-analysis, the authors demonstrated a clearer, nonbeneficial effect of AOT, thereby questioning its relevance in the management of CP pain. Although the authors have used a robust and strict inclusion criterion to obtain their current sample studies, it should be noted that the results are influenced by the addition of one randomized clinical trial, and thus, it may be premature to discourage the use of AOT. As the previous reviews and meta-analyses highlight a weak signal despite overcoming the noise of heterogeneity arising from various studies, clinicians and scientists should not ignore its role in CP pain management yet.

This study by Mohta et al. helps us to refocus our attention on a more important question: “Why do such discrepancies exist in efficacy of AOT in pain control?”. Possible factors include heterogenous disease course, differences in study population, patient demographics, and etiological and morphological disease profile. In addition, there are multiple confounding factors, such as smoking, malnutrition, subjective pain scales, varying use of AOT dose, and composition, which differ among different studies and are difficult to control for in meta-analyses.4–7 To overcome this challenge, one may propose to develop and apply a series of filters on existing databases from various studies to define and enrich a subset of population that may potentially benefit from AOT. Furthermore, as the management of pain in CP is a multimodal approach (addressing inflammation + structural abnormality and visceral hypersensitivity/chronic pain), in the future, AOT trials may have to carefully exclude patients with visceral hypersensitivity/chronic pain who are often refractory to pain management therapies.

Thus, the results of this review and meta-analysis should be taken in proper context so as not to disrespect a potentially useful therapy, which has a sound scientific basis. It may be tempting to take the position that AOT does not have a role in the pain management of CP across the spectrum. However, it may be more helpful to identify key opportunities that will refine the understanding of the ideal patient population that may benefit the most from AOT. This could be done by either modeling or discovering potential biomarkers and should be the next step forward in understanding the role of antioxidants in CP.

Ayush Sharma and Ajay Kumar ©
Department of Gastroenterology and Hepatology, BLK Institute of Liver and Digestive Diseases, New Delhi, India

Correspondence
Ajay Kumar, Department of Gastroenterology and Hepatology, BLK Institute of Liver and Digestive Diseases, Pusa Road, New Delhi 110005, India.
Email: ajaykge@hotmail.com

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