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Review Article

A narrative review on rebound acid hypersecretion due to long-term use of proton pump inhibitors

Vysheshika Balivada[1], Ruttuja Mayuraysh Koraykar[1]

[1]Practice of Medicine, Bharathi Vidhyapeeth (Deemed to be) University Homoeopathic Medical college and Hospital, Pune, Maharashtra, India.

ABSTRACT

Objectives: Proton pump inhibitors (PPIs) are the most commonly used drugs to reduce hyperacidity. The usage of PPIs reduces the secretion of gastric juice; their prolonged usage results in gastric acid suppression with hypergastrinemia while their stoppage results in hypersecretion of gastric juice. This kind of paradoxical reaction is seen in the rebound effect of drugs. Dr. Samuel Hahnemann gave us the vital principles of homeopathy, the law of similitude, i.e., "similia similibus curentur" derived from the "Nature's Law of Cure". This also tells us that the primary action of medicine stimulates the dynamic expression of an organism (vital force), which results in the counteraction called secondary action by the organism.

Material and Methods: Review of literature on the effects of long-term use of PPIs and rebound hypersecretion of gastric juice due to PPIs.

Results: For this review article, 16 most relevant articles are selected from the search results. Thirteen systematic reviews, two randomized control trials, and one pilot study are included. Rebound acid hypersecretion (RAHS) occurs after prolonged treatment with histamine-2 blockers and PPIs, causing gastric hypoacidity and hypergastrinemia. Longer PPI durations can result in prolonged hypersecretion, with moderate hypergastrinemia and increased enterochromaffin-like (ECL) cell hyperplasia. Deprescribing PPIs is crucial to reduce RAHS and safety concerns. Long-term usage can lead to nutritional deficiencies, respiratory infections, and bone fractures.

Conclusion: Homeopathic remedies have shown significant results in treating symptoms caused due to gastritis, ulcers, gastroesophageal reflux disease, etc., and further research is needed to reduce RAHS caused due to the long-term use of PPIs.

INTRODUCTION

"Proton pump inhibitors (PPIs)" are a class of medicines that are most prominently known for their use in acid-related disorders. They include Omeprazole, Esomeprazole, Lansoprazole, Pantoprazole, Rabeprazole, and Dexrabeprazole.[1] H+-K+-ATPase plays a major role in the final step of acid secretion and this led to the development of PPIs. These drugs specifically target this H+/K+ ATPase enzyme in the proton pump. In the management of acid-peptic diseases, PPIs have displaced H2 blockers, as their fundamental pharmacological effect is the dose-dependent inhibition of gastric acid secretion without having any anticholinergic or H2 blocking effects. PPIs completely suppress Hydrochloric acid (HCI) secretion, both at rest and when stimulated by food or any of the secretagogues, in addition to inhibiting the secretion of gastric acid, without much effect on the gastric motility volume of gastric juice and other hormonal factors that influence the gastric acid secretion.[1]

Due to recent lifestyle modifications, most individuals are facing challenges regarding gastric complaints. To combat those symptoms, PPIs are used. Easy availability of this medication over the counter without any prescription and immediate relief of symptoms regardless of the recurrence led to the relentless usage of PPIs. This long-term use and abrupt stoppage of PPIs ultimately results in various side effects and complications in many individuals. The withdrawal of these medications must be attempted for patients who are receiving PPI therapy for uncertain symptoms or in situations where there is a minimal indication for PPI use. Rebound acid hyper-secretion (RAHS) is a condition where gastric acid production abruptly increases after a sudden discontinuation of PPIs. As a result, this could cause or exacerbate upper gastrointestinal (GI) symptoms. It's vital to avoid abrupt PPI withdrawal, especially in chronic users, and to implement a plan to decrease the RAHS phenomenon. Homoeopathic medicines are useful in the prevention and treatment of

***Corresponding author:** Dr. Vysheshika Balivada, Practice of Medicine, Bharathi Vidhyapeeth (Deemed to be) University Homoeopathic Medical college and Hospital, Pune, Maharashtra. Email: Vyseshika@gmail.com

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numerous diseases and can help us resolve the withdrawal symptoms of stopping PPIs.

Homoeopathy is a holistic system of medicine with the principle of similitude, i.e., "similia similibus curentur" (Like cures like), which is derived from the "Nature's Law of Cure". A homoeopathic remedy has mainly two effects, i.e., primary action and secondary curative action. The primary action is the initial response produced by the remedy when it is administered. This response is often an aggravation or intensification of the existing symptoms. This aggravation is considered a positive sign in homeopathy, indicating that the remedy has been properly matched to the individual's symptoms. Secondary action is the curative action or the desired therapeutic effect that occurs after the primary action subsides. Following the initial aggravation, the body's self-healing mechanisms are stimulated, and the symptoms gradually improve. The secondary action involves a restoration of the body's balance and resolution of the underlying cause. It's important to understand that the primary action is a transient and temporary exacerbation of symptoms, while the secondary action leads to long-lasting improvement and healing. The primary action is considered a necessary step in the curative process of homeopathy, as it indicates that the remedy is actively interacting with the body's vital force and stimulating the healing response. It's worth noting that not all individuals experience a noticeable primary action with each homeopathic remedy. The intensity and duration of the primary action can vary depending on the susceptibility of the individual and the nature of the complaint being treated. Homeopathy aims to stimulate the body's innate healing abilities, and the primary and secondary actions are integral parts of the healing process within this holistic approach.

Dr. Samuel Hahnemann presents several instances of primary action and the vital force's secondary curative action. The vital force acts instinctively to maintain homeostasis while simultaneously causing potent and antagonistic symptoms to the initial alteration of vitality. Hahnemann's Organon of Medicine, paragraph 65 states that "*Excessive vivacity follows the use of strong coffee (primary action), but sluggishness and drowsiness remain for a long time afterward (reaction, secondary action) if this be not always again removed for a short time by imbibing fresh supplies of coffee (palliative). After the profound stupefied sleep caused by opium (primary action), the following night will be all the more sleepless (reaction, secondary action). After constipation produced by opium (primary action), diarrhea ensues (secondary action), and after purgation with medicines that irritate the bowels, constipation of several days" duration ensues (secondary action). And in like manner, it always happens, after the primary action of a medicine that produces in large doses a great change in the health of a healthy person, that it is the exact opposite when, as has been observed, there is actually such a thing, is produced in the secondary action by our vital force*".[2] In a similar manner, initially, when patients use PPIs to reduce gastric acidity, primary action acidity decreases, but whenever the medicine is stopped in secondary action, it results in an increase in the secretion of acid by the parietal cells. In a similar way, RAHS is the organism's secondary action to the prolonged use of PPIs.

MATERIAL AND METHODS

The literature in books is referred to, and search engines like Google Scholar, ResearchGate, and PubMed databases are used along with the keywords proton pump inhibitors, rebound hypersecretion, randomized control trials, and literature in homoeopathy to select the scientific evidence in the most relevant articles.

RESULTS

Physiology of gastric acid secretion

The stomach is lined with mucous cells, parietal cells, chief cells, and neuro-endocrine cells (G-cells, ECL-like cells, and D-cells). Each of the cells has its specialized function. The mucus cells produce mucus, which functions as a protective barrier from the acidic pH of the gastric juice. The parietal cells secrete the intrinsic factor and HCl. Vitamin B12 absorption in the small intestine depends on the intrinsic factor. HCl helps with the digestion of proteins and kills the bacteria present in the food. Chief cells secrete the pro-enzyme pepsinogen, which is essential for the digestion of proteins after its conversion to pepsin by HCl. G-cells produce a neuroendocrine hormone called gastrin, which increases HCl production both directly and indirectly. The ECL-like cells produce histamine, which indirectly increases HCl production. D-cells secrete somatostatin (SST), an inhibitory hormone that decreases the production of gastric acid by inhibiting the secretion of gastrin.

Gastric acid secretion is a multi-step, complicated process. Acetylcholine (ACh), histamine, and gastrin synergistically stimulate acid release. Vagal stimulation caused due to sight, smell, or the presence of food causes the release of ACh. It stimulates the nicotine receptor (N) and muscarinic receptor (M1) in the enteric nervous system (ENS ganglion cell). The postganglionic ENS neurons release gastrin-releasing peptide (GRP) and ACh. Stretch receptors are stimulated with distension of the stomach due to the presence of food; raising pH activates the chemoreceptors; along with the stimulation by stretch receptors and chemoreceptors, GRP and ACh also act on G-cells, facilitating the release of the hormone "gastrin". ACh also stimulates the muscarinic receptors (M, M3), and gastrin stimulates the cholecystokinin (CCK2) receptors on

the ECL cells and parietal cells. Gastrin and ACh aid in the production of HCl's direct and indirect mechanisms. ACh indirectly inhibits SST secretion, thus promoting gastric acid secretion. The hormone "histamine" is secreted by ECL cells with the stimulation of M and CCK2 receptors which stimulates H2 receptors on parietal cells, thus stimulating the adenylate cyclase (AC), generating cAMP in the parietal cell lumen, aiding indirectly in the secretion of HCl. The direct mechanism involves the direct stimulation of parietal cells. The stimulated M3 increases the intracellular calcium, and the phospholipase C is activated by CCK2 receptors to increase the cytosolic calcium release. Both mechanisms increase H+K+ ATPase activity. The proton pump, H+K+ ATPase, is activated in the lumen of the parietal cell by downstream protein kinases that are triggered by intracellular calcium and cAMP-dependent signaling pathways. H+K+ ATPase catalyzes the electro-neutral exchange of luminal K+ for the cytoplasmic H+. This reaction is coupled with the extrusion of Cl- and K+ ions through an apical chloride channel and apical potassium channel, thus producing HCl. ACh indirectly inhibits the secretion of SST, which is mediated by the inhibition of atrial natriuretic peptide (ANP) secretion from ECL cells. Vasoactive intestinal peptide (VIP)-expressing neurons are activated by distension of the stomach and stimulate SST and Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP) neurons, and the release of ANP also stimulates the release of SST and, thus inhibits gastric secretion.[3–8]

Pathophysiology

Peptic ulcer: Ulceration is caused due to any kind of imbalance between the gastric mucosal defending factors and aggressive factors.[1] Pepsin and HCl are the aggressive factors, whereas neuropeptide Y, calcitonin, neurotensin, prostaglandins, interleukin 1, corticotropin-releasing factor, bicarbonates, mucin, and neurotensin are the defending factors.[9] Treatment includes restoring the balance between these aggressive and defending factors. Duodenal ulcers (DU) are caused due to secretary abnormalities. Average basal and nocturnal gastric acid secretion appears to be increased in DU10. Gastric ulcers (GU) are caused due to weakening of the mucosal defense mechanisms. The majority of GUs are caused by either H. pylori or Nonsteroidal antiinflammatory drug (NSAID)-induced mucosal damage.[10] Ulcer formation, GI bleeding, or related perforation is at a 2–4% risk in chronic NSAID users. NSAIDs quadruple the risk of potential complications in ulcer patients.[9] PPIs and H2-receptor antagonists aid in preventing and managing the relapse of peptic ulcers.

Gastroesophageal reflux disease (GERD): It results from the normal anti-reflux barrier failing to protect against persistent and excessive gastroesophageal reflux. It is caused due to esophageal injuries, adenocarcinoma, stricture, and Barrett's esophagus.[11] In healthy people, gastroesophageal reflux episodes happen occasionally. The esophageal peristaltic waves that often follow reflux effectively evacuate the gullet, alkaline saliva neutralizes any remaining acid, and symptoms are avoided. When the esophagus mucosa is exposed to gastroduodenal contents for extended periods of time, then GERD occurs and, in some instances, esophagitis. It is recognized that a number of factors contribute to the onset of GERD.[12] The main causes of GERD are defective anti-reflux barriers like hiatus hernia (sliding type), abnormalities of the lower esophageal sphincter which causes relaxation and reduction of the lower esophageal sphincter's tone, and cardiomyotomy and vagotomy also reduce the efficiency of the lower esophageal sphincter. Drugs like aminophylline, beta-agonists, nitrates, and calcium channel blockers also reduce lower esophageal sphincter (LES)'s tone. Crural diaphragm, increased intra-abdominal pressure, and prolonged/delayed esophageal clearance of refluxed acid in which there is impaired peristalsis, reduced salivation, and body position cause GERD. Insufficient esophageal clearance causes a longer period of acid exposure. Defective gastric emptying increases the amount of stomach content available for reflux. The potential causes are anticholinergic medicines, fatty meals, and obstruction of the gastric sphincter.[11]

Esophagitis: Despite having completely normal appearances, one can recognize a wide range of endoscopic findings. These findings can be limited to mild redness or severe bleeding ulceration with stricture formation. The symptoms and histological and endoscopic findings have a proper correlation between them.

Barrett's esophagus: Barrett's esophagus is a premalignant condition. In this condition, a columnar mucosa replaces the normal squamous lining of the lower esophagus. It may have certain areas of intestinal metaplasia. Among all the patients undergoing gastroscopy for reflux symptoms, 10% of them may have it as an adaptive response to chronic gastroesophageal reflux. It can be associated weakly to smoking but not with alcohol intake. The danger of cancer appears to relate to the brutality and duration of reflux rather than the presence of Barrett's esophagus, and it has been advised that duodenogastro-esophageal reflux of bile, pancreatic enzymes, and pepsin, as well as gastric acid, will be significant in the pathogenesis.

Zollinger–Ellison syndrome (Z-E syndrome): Gastrin may be produced by non-b-cell tumors of the pancreatic islets in quantities high enough to promote the release of stomach acid. Uncontrolled hyperchlorhydria results in serious gastroduodenal ulcerations and other problems. The treatment goal is to reduce the

hypersecretion of gastric acid. PPIs are unquestionably the drug of choice. The controlling of hyperacidity in Z–E syndrome is done more effectively by Omeprazole than by histamine H2-receptor antagonists (H-2 blockers).

DISCUSSION

Generally, the RAHS can be simply represented as the increased acid secretion seen after a definite period of acid suppression. This RAHS has been recorded after treatment with H-2 blockers as well as PPIs. PPI causes gastric hypoacidity associated with hypergastrinemia. Unremitting stimulation of the ECL cells causes hypergastrinemia and hyperhistaminemia without increasing gastric acidity because the proton pump is effectively blocked. Continuous stimulation of the ECL cells causes the proliferation of the ECL cell mass. When the drug is discontinued, the mass effect is noticed to persist longer than the effect of actual PPI. Rebound hypersecretion occurs after 2 weeks from the sudden stoppage of prolonged PPI treatment until the ECL cell mass is restored to normal. Due to a potential impact on the parietal cell mass, lengthier PPI treatment durations are anticipated to result in longer RAHS.[13] These findings are also seen in *Helicobacter pylori*-positive patients with noticeably amplified gastrin levels. If the acid release is intact, *H. pylori* colonizes predominantly in the gastric antrum, causing antral-predominant gastritis, and if acid release is suppressed (by using PPIs), it colonizes in the body of the stomach, causing corpus-predominant gastritis. Inflammation of the antral mucosa causes increased production of gastrin, maintaining the acid production. However, inflammation in the antrum further impairs acid secretion and causes hypergastrinemia.[14] A systematic review done by L. Lundell *et al.* showed that long-term PPI therapy brought about reasonable hypergastrinemia in most patients and also an increased prevalence of ECL cell hyperplasia. It also shows that *H. pylori*-positive patients receiving long-term PPI therapy have a higher risk of corpus atrophy than *H. pylori*-negative patients.[15]

A randomized, double-blind, placebo-controlled trial done by Christina Reimer *et al.* with 120 healthy volunteers was conducted. The first group is given eight weeks of Esomeprazole 40 mg/day followed by four weeks of placebo, and the second group is given 12 weeks of placebo. Weekly symptom evaluations were done using the Gastrointestinal Symptom Rating Scale (GSRS). A score > 2 (equivalent to symptoms causing mild to severe discomfort) for heartburn, regurgitation, and dyspepsia indicates a clinically relevant acid-related symptom. Results showed that there were significantly higher GSRS scores for acid-related symptoms in the PPI group at week 10 (1.4 1.4 vs. 1.2 0.9; P = .023), week 11 (1.4 1.4 vs. 1.2 0.9; P = .009), and week 12 (1.3 +/- 1.2 vs 1.0 +/- 0.3; P = .001). In weeks 9–12, 44% of those randomly assigned to PPI reported one acid-related symptom versus 15% in the placebo group. In the PPI group, 13 of 59 patients (22%) at week 10, 13 of 59 patients (22%) at week 11, and 12 of 58 patients (21%) at week 12 reported having dyspepsia, heartburn, or acid regurgitation. Accordingly, the placebo group's numbers at weeks 10 (P = .034), 11 (P = .013), and 12 (P = .001) were 7%, 5%, and 2%, respectively. This study highlights overlooked PPI withdrawal symptoms and adds credibility to the hypothesis that RAHS has clinical consequences.[16] This study shows that the usage of PPI without a clear indication can cause RAHS symptoms even in healthy human beings. PPI consumption, which has spread like a disease around the world, remains to be exacerbated by excessive and improper prescribing of PPIs in daily practice. Physicians should take great care while prescribing PPIs in their everyday practice. These include a written indication, a treatment duration plan, and a defined review date to reassess the necessity for continuous treatment.[17]

The purpose of the randomized control trial by Andres Vales *et al.* was to evaluate how structured alginate use affected the severity of symptom burden in GERD. Forty-eight participants, who were receiving PPI therapy for about four weeks, were referred for manometry and 24-hour pH/impedance testing. PPIs and H2 receptor antagonists had to be stopped for a week, and antacids and alginates were permitted to be used up until the night before the course of the probe. The treatment group received the same instructions while taking Gaviscon Advance four times per day, while the control group was randomly assigned to follow the standard instructions. Gastro-Esophageal Reflux Disease Health-Related Quality of Life Score change was the main outcome assessed. The findings demonstrated that structured alginate use prevents symptom exacerbation during pre-investigation PPI washout, which is advantageous for thousands of patients each year who are being investigated for gastroesophageal reflux. To evaluate this impact in more detail, additional research is sustained on PPI deprescription.[18]

Deprescribing PPIs is also important to reduce RAHS due to extensive usage of PPIs and their associated safety considerations. As mentioned by Helgadottir H *et al.* in deprescribing studies, various interventions can be used to reduce a patient's PPI dosage by up to 80%, and about 30% of patients on long-term PPI therapy can discontinue long-term PPI therapy.[17] When there is no indication for long-term therapy, PPI deprescribing should be taken into consideration. Evidence points to a patient-centered strategy that calls for decreasing the dose before stopping or switching to PRN (as required) use. A gradual dose tapering before discontinuation can minimize the risk of short-term RAHS, which can be treated on-demand (PRN). Patients should be

involved in the development of the deprescribing plan as well as the discussion of the reasons for deprescribing.[19]

A study done by Fossmark R *et al.* showed that patients with anti-reflux surgery who used PPIs for over a year discontinued acid-suppressing drugs after the operation. Postoperatively, basal and pentagastrin stimulated acid output was measured, and oxyntic mucosal biopsies were collected for histidine decarboxylase (HDC) immunoreactive cells. Results showed higher pentagastrin-stimulated acid secretion at 4 and 8 weeks, reduced gastrin and CgA at 4 and 8 weeks, and a 60% reduction in HDC immunoreactive cells at 26 weeks postoperative.[20]

The systematic review done by Teixeira MZ *et al.* showed evidence that the acid rebound happens 1 hour after using antacids, 2 days after taking H2-receptor antagonists for weeks, and 1–2 weeks after taking PPIs for 4–8 weeks. After 4 weeks of H2-receptor antagonists, the rebound phenomenon lasts for 10 days; after 4 or 8 weeks of PPIs, it lasts for 2 or 4 weeks. RAHS was reported by almost 40% of PPI users. The American Hospital Formulary Service reported that 41% of patients experienced a recurrence of peptic ulcers after ceasing their long-term cimetidine medication after 1–4 weeks.[21, 22] One study published in the journal *Gut* in 2009 found that patients who stopped taking PPIs after 8 weeks of treatment experienced a significant increase in acid production, with symptoms of heartburn and acid regurgitation returning in many patients within 2weeks. However, the study also found that the rebound effect was generally mild and transient, lasting for only a few weeks. Another study published in the *American Journal of Gastroenterology* in 2013 looked at the rebound effect in patients who had been taking PPIs for 6 months or longer. The study found that patients who stopped taking PPIs experienced a significant increase in acid production, with symptoms returning in many patients within a week. However, the study also found that the rebound effect was generally mild and that most patients were able to successfully manage their symptoms with lifestyle modifications.

Due to the prevalent usage of these medications and their large margin of safety, prolonged PPI use has been a major cause for concern. Long-term PPI usage, however, raises questions about potential negative consequences, including an elevated risk of respiratory infections, clostridium difficile infection, and bone fractures. PPIs have negligible renal clearance and a rapid first-pass and systemic hepatic metabolism by hepatic cytochrome P, notably cytochrome P2C19 and cytochrome P3A4. PPIs typically have minor side effects, with headaches, nausea, abdominal pain, constipation, flatulence, and diarrhea being the most frequent ones. However, PPI side effects over the long run have recently received more attention, and numerous studies have examined a range of side effects that could be related to long-term PPI use. Long-term effects include nutritional deficiencies like vitamin B12 deficiency, iron deficiency, and calcium deficiency with a risk of osteoporosis and hypomagnesemia, risk of infections like clostridium difficile infections and other enteric infections, risk of respiratory infections like community-acquired pneumonia, kidney disease, and acute kidney injury. It can also cause hypergastrinemia and malignancy like gastric polyps, gastric cancer, colon cancer, etc.[15,23,24]

HOMOEOPATHY

A review done by Debjit Bhowmik *et al.* on peptic ulcers showed that homeopathic medicines like argentum nitricum, arsenicum album, kali bichromicum, lycopodium, nitric acid nux vomica, phosphorus, pulsatilla, etc., help to eliminate the symptoms caused by *H. pylori* by healing the ulcers.[25] Another review article done on the management of peptic ulcer through homoeopathy by Partha Ratnaparikh and Sonika S. Adkine in Guru Mishri Homoeopathic Medical College PG Institute also showed that homoeopathic medicines are very helpful in treating ulcers.[26] A pilot study done by Mittal R *et al.* on nonerosive gastroesophageal reflux disease (NERD) characterized by reflux-related symptoms without esophageal erosions showed that homoeopathic medicines were used to treat symptoms like heartburn and regurgitation and found that homoeopathic medicines were effective in treating NERD. This study involved 78 patients with heartburn and/or regurgitation symptoms and a GERD symptom score of more than 4. Results showed significant differences in GERD symptom scores and VAS for heartburn, as well as improvements in psychological health, social relationships, and environmental domains. These findings suggest that further studies on reflux disease may be beneficial.[27] A review done on the scope of homeopathic management in gastritis by Akhila Doppalapudi and Shankar Hulekar showed that homoeopathic medicines like abies Canadensis, arsenic album, argentum nitricum, bismuthum, bryonia alba, chamomilla, cantharis ves, carbo veg, ipecac, nux vomica, phosphorus, lycopodium clav, etc., showed significant results in the management of gastritis.[28]

CONCLUSION

RAHS occurs after a period of acid suppression, often seen after treatment with histamine-2 blockers and PPIs. PPIs cause gastric hypoacidity and hypergastrinemia, while continuous stimulation of ECL cells causes hypergastrinemia and hyperhistaminemia without increasing gastric acidity. Rebound hypersecretion occurs after two weeks of prolonged PPI treatment until the ECL cell mass restores to normal. Longer PPI treatment durations are expected to result in

longer RAHS. Long-term PPI therapy can cause moderate hypergastrinemia and increased prevalence of ECL cell hyperplasia, with *H. pylori*-positive patients having a higher risk of corpus atrophy. Deprescribing PPIs is crucial to reduce RAHS and safety concerns. Gradual dose tapering can minimize short-term RAHS risk. Patients should be involved in the deprescribing plan and discuss reasons for deprescribing. RAHS occurs 1–2 weeks after taking PPIs for 4–8 weeks. Long-term usage of PPIs has potentially negative consequences like nutritional deficiencies, elevated risk of respiratory infections, clostridium difficile infection, and bone fractures. Homoeopathic remedies showed significant results in treating the symptoms caused due to hyperacidity, ulcers, GERD, etc. Further research should be done on the homoeopathic treatment of gastric symptoms to reduce the long-term usage of PPIs.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

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Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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