Exploring methods for treating hypergastrinemia in patients with autoimmune atrophic gastritis: A prospective study.

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Protocol Version Number: 1.0

Version Date: January 30, 2024

1.Title of the Study

Exploring Methods for Treating Hypergastrinemia in Patients with Autoimmune Gastritis: A Prospective Study.

2.Research Background

Autoimmune atrophic gastritis (AAG) is an organ-specific autoimmune disease that primarily affects the gastric body and fundus, while sparing the antrum[1]. Its characteristics include destruction of gastric wall cells, loss of intrinsic factor, and atrophy of the gastric mucosa. Endoscopic examination reveals features of reverse atrophy, with significant atrophy in the gastric body and fundus, appearing as a mosaic of red and white patches, predominantly white, with flattened and partially disappearing folds and visible blood vessels[2]. Currently, AAG is believed to result from a pathological CD4+ T-cell-mediated autoimmune response against the gastric H+/K+-ATPase[3]. CD4+ T lymphocytes target the parietal cells' H+/K+-ATPase, stimulating plasma cells to secrete autoantibodies, including parietal cell antibodies (PCA) and intrinsic factor antibodies (IFA)[4]. The former play a key role in parietal cell destruction and glandular atrophy, while the latter are the main mechanism underlying vitamin B12 deficiency and pernicious anemia[5]. AAG is considered a premalignant condition, with potential development of gastric dysplasia, cancer, and type 1 gastric neuroendocrine tumors (type 1 g-NET) [6]。

Gastric neuroendocrine tumors (g-NETs), also known as gastric carcinoids, account for approximately 23% of gastrointestinal and pancreatic neuroendocrine tumors[7]. Clinically, g-NETs are mainly classified into three types[8], Type I and type II are associated with chronic atrophic autoimmune gastritis[9] and gastrinoma-related Zollinger-Ellison syndrome (ZES) leading to hypergastrinemia, while type III is typically sporadic tumors associated with normal gastrin levels and poor prognosis[10]. Although type 1 g-NETs caused by AAG are usually well-differentiated, studies have reported that 8%-23% of type 1 g-NETs extending into the deep submucosal layer may metastasize to regional lymph nodes or even to the liver[11]. Furthermore, 3% of patients may develop neuroendocrine carcinoma[12], highlighting the need for appropriate attention.

Due to the destruction of gastric glands (including parietal and chief cells) in AAG patients, there is a deficiency in intrinsic factor, gastric acid, and a decrease in pepsinogen I (PG-I) levels. Insufficient gastric acid secretion leads to a compensatory increase in gastrin secretion by G cells in the gastric antrum, which acts on receptors present on enterochromaffin-like cells (ECL) in the gastric body and fundus, promoting ECL cell proliferation[13]. Prolonged stimulation by hypergastrinemia can result in the development of ECL cell tumors, namely type 1 g-NETs[14, 15]. Considering the close association between type 1 g-NETs and AAG, primarily related to hypergastrinemia resulting from reduced gastric acid secretion, it is hypothesized that supplementation with gastric acid could provide negative feedback regulation of gastrin, reducing the risk of type 1 g-NET development in AAG patients. This study aims to investigate the impact of Betaine hydrochloride (BHCL) on gastrin levels in AAG patients, thus exploring a simple and cost-effective method to reduce the risk of type 1 g-NETs in AAG patients.

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3.Research Objectives

(1) To investigate the safety and efficacy of Betaine hydrochloride (BHCL) in treating hypergastrinemia in patients with autoimmune gastritis, aiming to use a convenient and feasible approach to reduce the risk of type 1 gastric neuroendocrine tumors in patients with autoimmune gastritis.

(2) To further enhance understanding of autoimmune gastritis and type 1 gastric neuroendocrine tumors.

4.Study Content

(1) Study Population and Clinical Data

We conducted a prospective study at the First Affiliated Hospital of Zhengzhou University, involving patients diagnosed with autoimmune atrophic gastritis (including outpatients and inpatients). Each participant was assigned a unique identification number and randomized into one of three groups using a random number table. Group A received only oral administration of placebo; Group B received only oral administration of a compound digestive enzyme capsule; and Group C received only oral administration of Betaine hydrochloride（BHCL). Blood samples were collected from each participant before the start of the trial and three months after the trial to measure serum gastrin levels. The gastrin levels before and after the trial were compared within each group, and the differences in gastrin levels between the post-trial and pre-trial measurements were compared among the groups.

(2) Inclusion Criteria:

1) Patients diagnosed with autoimmune atrophic gastritis at the First Affiliated Hospital of Zhengzhou University, using the diagnostic criteria from the "Guidelines for the Diagnosis and Treatment of Chronic Gastritis in China (2022, Shanghai)" for the diagnosis of atrophic gastritis, combined with serum gastrin, PCA, or IFA for the diagnosis of autoimmune atrophic gastritis.

2) Patients who have signed the informed consent form for the clinical trial.

(3) Exclusion Criteria:

1) Patients with Betaine hydrochloride (BHCL) allergies.

2) Patients with gastric ulcers, gastroesophageal reflux disease, or cholelithiasis, as the administration of acid agents may worsen the condition or cause discomfort.

3) Patients with gastrinomas or other conditions that can cause elevated gastrin levels, apart from autoimmune atrophic gastritis.

4) Patients who are unable to provide informed consent or sign the informed consent form.

(4) Research Methods and Study Content:

1) Preparations before the trial: Prior to the trial, patients undergo serum gastric function testing and provide baseline serum gastrin levels.

2) Patients who meet the criteria are assigned unique identification numbers and randomized into three groups using a random number table. Group A receives only oral administration of placebo, with one capsule taken three times a day.Group B receives only oral administration of a compound digestive enzyme capsule, with one capsule taken three times a day. Group C receives only oral administration of Betaine hydrochloride（BHCL), with one capsule before each meal. Blood samples are collected before the start of the trial and three months after the trial to measure serum gastrin levels. The gastrin levels before and after the trial are compared within each group, as well as the differences in gastrin levels between the post-trial and pre-trial measurements among the groups.

3) Collection of patient data:

- General information: Height, weight, gender, age, smoking and drinking habits, presence of hypertension or diabetes, and whether first-degree relatives have gastric cancer. - Specific information: Serum gastrin levels of each group of patients before and three months after the trial; adverse reactions (such as abdominal pain, bloating, acid reflux, heartburn) reported by patients during the three-month follow-up after taking Betaine hydrochloride（BHCL).

4) Calculation and analysis of data:

- Comparison of serum gastrin levels before and after the trial within each group.

- Comparison of the differences in serum gastrin levels between the post-trial and pre-trial measurements among the groups.

- Calculation and comparison of the adverse reaction rates after three months of the trial in each group: Adverse reaction rate = Number of patients with adverse reactions in each group / Number of patients examined in each group.

5) Statistical methods: Statistical analysis is performed using SPSS 26.0 software. Count data are presented as frequency (n) and percentage (%), and comparisons between groups are analyzed using the chi-square test, chi-square' test, or Fisher's exact test. Measurement data are presented as mean ± standard deviation, and comparisons between groups are analyzed using the t-test, t'-test, or non-parametric tests (Mann-Whitney U test). A significance level of $P < 0.05$ is considered statistically significant.

5.Expected Research Outcomes

(1) Investigate the safety and efficacy of oral administration of Betaine hydrochloride(BHCL) in treating hypergastrinemia in patients with autoimmune atrophic gastritis, aiming to reduce the risk of developing type 1 gastric neuroendocrine tumors in individuals with autoimmune atrophic gastritis.

(2) Publish one scientific research paper in a SCI-indexed journal.

6.Research Ethics Considerations

（1） (1) Privacy Protection: The collected patient data will be used solely for the purpose of this research. Patient information collected during the study will be kept confidential. For example, clinical data will be identified by a research identification number rather than the patient's name. Information that can identify the patient will not be disclosed to anyone outside of the research team without the patient's permission. All research team members and sponsors are required to maintain the confidentiality of patient identities. Patient records will be stored securely in filing cabinets and accessible only to authorized research personnel. Government regulatory authorities or ethics review committees may have access to patient information at the research site to ensure compliance with regulations. When publishing research results, no personally identifiable information of patients will be disclosed.

(2) Informed Consent: All participants involved in the study will be fully informed about the risks and benefits and will sign an informed consent form before participating in the research.