Nizatidine and Acotiamide: New Treatment Combination for Functional Dyspepsia?

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Dyspepsia is a common presenting symptom in patients for gastroenterologists. Dyspepsia is often defined as a variety of symptoms thought to be originating from the gastroduodenal region in the upper gastrointestinal tract.[1] This can include symptoms such as epigastric pain, burning, postprandial fullness, and early satiation.[2] The prevalence of dyspepsia worldwide is about 21%, though it varies based on the definitions. In South East Asia, the prevalence is about 14%.[3] Based on the endoscopic findings, dyspepsia can be caused by organic etiologies or functional dyspepsia. In functional dyspepsia, no pathology was identified during the endoscopic exam. Based on a meta-analysis, the prevalence of normal findings in patients with dyspepsia is around 85%.[4]

The ROME IV criteria were developed to identify and classify patients with functional dyspepsia. The criteria for entry are patients with one of the dyspepsia symptoms (bothersome postprandial fullness, early satiation, epigastric pain, or burning) and no evidence of structural disease that can explain the symptoms. The criteria must be fulfilled for the last 3 months, and the symptom onset must be at least 6 months before diagnosis.[5] Based on this definition, the global prevalence of functional dyspepsia is around 7.8%. The estimated prevalence in Indonesia is 4.4%.[6]

Based on the predominant symptoms, patients with functional dyspepsia can be further classified into postprandial distress syndrome or epigastric pain syndrome. Patients with functional dyspepsia often have other gastrointestinal comorbidities. The Asia Pacific guideline identified four functional dyspepsia overlap symptom clusters: functional dyspepsia with gastroesophageal reflux disease (FD-GERD), epigastric pain syndrome with irritable bowel syndrome (EPS-IBS), postprandial distress syndrome with IBS (PDS-IBS), and functional dyspepsia with constipation (FD-Constipation).[7]

The pathophysiology of functional dyspepsia is disorders in brain-gut interaction, which lead to impairments in gastric accommodation, emptying, and motility. Patients with functional dyspepsia also have visceral hypersensitivity.[8] Other possible mechanisms include local immune activation, abnormal intestinal microbiota, genetic polymorphisms, psychosocial factors, and abnormal processing of visceral signals in the central nervous systems.[9]

Although a definitive diagnosis of functional dyspepsia is based on the exclusion of endoscopic findings, it is not recommended to perform endoscopy in every patient with dyspepsia. In most cases, functional dyspepsia can be diagnosed clinically in young patients without alarm signs. The 2017 American College of Gastroenterology guidelines recommend endoscopy in patients aged ≥ 60 years old. The guideline also stated that patients <60 years old did not need upper GI endoscopy, even if alarm signs were present, because the prevalence of gastric cancer was still low in that age group. However, if the alarm signs are prominent (e.g., weight loss >10 kg or rapid progressive dysphagia), then endoscopy is recommended.[10] Meanwhile, the Japanese guideline recommends endoscopy in patients with alarm signs due to the higher prevalence of gastric cancer.[8] Similarly, the British guideline recommends urgent upper GI endoscopy in patients with alarm signs, patients aged ≥ 55 years old with dyspepsia and weight loss, or patients ≥ 40 years old from an area with an increased risk of gastric cancer or with a family history of gastroesophageal cancer.[11] In addition, all guidelines suggest non-invasive tests to detect *Helicobacter pylori*. If patients are tested positive, then eradication therapy following the latest guideline is recommended.[12] Other tests that can be performed include complete blood count, celiac serology, and imaging, especially in patients suspected to have pancreatic cancer.[11]

The treatments of functional dyspepsia involve pharmacological and non-pharmacological measures. Non-pharmacological interventions include avoidance of simple dietary triggers, regular aerobic exercise, and psychotherapy.[11] Pharmacological classes that are used to treat functional dyspepsia include: acid-suppressive drugs (proton pump inhibitor, histamine type 2 receptor antagonist, potassium-competitive acid blockers), prokinetic agents, fundus-relaxing agents (e.g., acotiamide, 5-HT receptor 1A agonist), and centrally-active neuromodulators (e.g., tricyclic antidepressants).[9] For patients who are *H.pylori*-negative, most guidelines recommend empiric therapy using proton pump inhibitors (PPIs) as the first-line treatment.[8, 10, 11] For patients refractory to PPIs, then tricyclic antidepressants or prokinetics can be given to the patients. In patients with postprandial distress syndrome subtype, prokinetics can be given as first-line treatment.[1, 9] The Japanese guideline also recommends rikkunshito (a type of Japanese herbal medicine) as a first-line treatment for functional dyspepsia.[8]

In this issue of *The Indonesian Journal of Gastroenterology, Hepatology, and Digestive Endoscopy*, an article by Kajihara Y[13] was published. The author conducted a study comparing the efficacy of two treatment regimens to treat functional dyspepsia in the Japanese population. The combination being investigated was nizatidine and acotiamide. The comparator is a combination of rabeprazole and acotiamide. Nizatidine is a histamine type 2 receptor antagonist (H_2RA). A recent meta-analysis showed that H_2RA and PPI had comparable efficacy.[14] Besides acid suppression, a small study in Japan reported that nizatidine can improve gastric emptying in functional dyspepsia.[15] Meanwhile, acotiamide is an acetylcholinesterase inhibitor that can lead to prokinetic effects. A previous meta-analysis showed that acotiamide can lead to higher rates of symptom improvements than placebo, although the difference was not statistically significant (OR = 1.48; 95% CI: 0.93 to 2.35).[16]

The study by Kajihara Y was conducted in a single institution, involving 66 patients with functional dyspepsia, of which 45 patients received the investigational regimen, and 21 patients received the comparator regimen. The results showed no significant difference in the rate of symptom improvement between the two groups. However, there are several limitations to this study. The sample size is small, and no formal sample size calculation is performed. The diagnosis of functional dyspepsia is not based on the Rome IV criteria. The author used the definition endorsed in the Japanese guideline, in which functional dyspepsia is defined as patients with chronic symptoms in the upper abdomen (epigastric pain or discomfort) in the absence of any organic disease etiology. The definition of discomfort and chronicity is left to the treating clinician. The rationale of this definition is that it captures more patients than the rigid ROME IV criteria. In addition, the two groups have some differences in the baseline characteristics. Despite that, the result of this study can inform future research regarding the use of nizatidine and acotiamide in patients with functional dyspepsia.

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