11. Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

Reference

Takeuchi T, Hongo H, Kimura T, et al. Efficacy and safety of hangeshashinto for treatment of GERD refractory to proton pump inhibitors: Usual dose proton pump inhibitors plus hangeshashinto versus double-dose proton pump inhibitors: randomized, multicenter open label exploratory study. *Journal of Gastroenterology* 2019; 1-12. Pubmed ID: 31037449, UMIN ID: UMIN000021251

1. Objectives

To determine the efficacy and safety of hangeshashinto（半夏瀉心湯）in treating patients with proton pump inhibitor (PPI)-refractory gastroesophageal reflux disease (GERD).

2. Design

Randomized controlled trial (RCT).

3. Setting

Seven hospitals, Japan (the author belongs to Osaka Medical College Hospital Endoscopy Center).

4. Participants

Seventy-eight patients with GERD refractory to a standard regimen containing PPI for at least 4 weeks.

5. Intervention

Arm 1: Combination of rabeprazole at a standard dose (10 mg/day) plus TSUMURA Hangeshashinto（半夏瀉心湯）Extract Granules (2.5 g three times daily for 4 weeks) (n=42).
Arm 2: Rabeprazole at a double dose (20 mg/day for 4 weeks) (n=36).

6. Main outcome measures

Primary end points of efficacy were the degree of improvement in the "Frequency Scale for the Symptoms of GERD (FSSG)" score, and the change in FSSG score over time. Secondary end points included acid-related dyspepsia (ARD) score and gastrointestinal-related QOL.

7. Main results

The analysis was conducted on 70 patients (i.e., 38 patients in Arm 1 and 32 patients in Arm 2) after exclusion of dropouts, etc. The change in the FSSG score showed no significant difference between the two groups. While the total FSSG score significantly decreased in both groups ($P < 0.001$), the ARD score in the hangeshashinto-combined group significantly decreased from Week 1 of treatment ($P < 0.05$). In the hangeshashinto-combined group, compared with the double-dose PPI group, the ARD score significantly improved in the subsets of patients with BMI <22 ($P< 0.05$) and age <65 years ($P< 0.05$).

8. Conclusions

Hangeshashinto may be beneficial for patients with PPI-refractory GERD, particularly in non-obese and non-elderly patients with dyspepsia symptoms.

9. From Kampo medicine perspective

The subgroup analyses for non-obese and non-elderly patients take the Kampo medicine concept of "*Kyojitsu* (*虚実*, deficiency and excess)" into account.

10. Safety assessment in the article

Adverse events that could be causally related to the treatment occurred in 3 of 38 patients in the hangeshashinto-combined group and none of 33 patients in the control group, with no significant difference in the incidence. The adverse events noted in the hangeshashinto-combined group were soft stool, nausea, and abnormal liver function.

11. Abstractor's comments

This RCT in GERD patients refractory to the standard dose of PPI is of value in that it showed earlier onset of symptomatic relief with the addition of hangeshashinto compared with a double-dose of PPI. Although the primary endpoint of "Frequency Scale for the Symptoms of GERD" showed no difference, absence of difference between adding Kampo medicine and doubling the PPI dose is meaningful from the viewpoint of the health economy. However, since this study used an open-label design, and the assessment scale was dependent on subjective symptoms, a placebo effect cannot be excluded. If the control group also used the standard dose of PPI, the primary endpoint of efficacy also could have shown a significant difference in favor of the hangeshashinto-combined group. Hangeshashinto is indicated for symptoms including belching and heartburn, which are also symptoms of GERD. This study provides evidence that supports recommending hangeshashinto in treating PPI-refractory GERD in non-obese and non-elderly patients.

12. Abstractor and date

Motoo Y, 28 August 2019.