## 18. Symptoms and Signs

**Reference**

Satoh N, Sakai S, Kogure T, et al. A randomized double-blind placebo-controlled clinical trial of hochuekkito, a traditional herbal medicine, in the treatment of elderly patients with weakness, N of one and responder restricted design. *Phytomedicine* 2005; 12: 549-54. CENTRAL ID: CN-00524047, Pubmed ID: 16121514

**1. Objectives**

To evaluate the efficacy of hochuekkito (補中益気湯) for the elderly with weakness.

**2. Design**

Double-blind, randomized controlled trial (DB-RCT) in combination with N-of-1 trial restricted to hochuekkito-responders.

**3. Setting**

Five hospitals associated with Toyama Medical and Pharmaceutical University (now Toyama University), Japan.

**4. Participants**

Fifteen elderly patients (3 males and 12 females; age [mean ± SD], 78.4±7.8 years) with weakness satisfying the following 4 inclusion criteria: (1) complaint of discomfort and anorexia due to chronic debilitating disease; (2) no history of infection or vascular disorder within 1 month before the start of the trial; (3) no malignant diseases; and (4) aged ≥60 years and <90 years.

**5. Intervention**

Responders during the 2-week run-in period were randomly assigned to the following 3 arms:

Arm 1: administration of Kanebo Hochuekkito (補中益気湯) Extract Fine Granules (2.5 g t.i.d.) before meals for 6 weeks followed by administration of the same dose of placebo at the same frequency for 6 weeks, with a 2-week washout between both administration periods (n=4).

Arm 2: administration of placebo (2.5 g t.i.d.) before meals for 6 weeks followed by administration of the same dose of Kanebo Hochuekkito (補中益気湯) Extract Fine Granules at the same frequency for 6 weeks, with a 2-week washout between both administration periods (n=5).

Arm 3: administration of Kanebo Hochuekkito (補中益気湯) Extract Fine Granules (2.5 g t.i.d.) before meals for 6 weeks followed by administration of the same dose of Kanebo Hochuekkito (補中益気湯) Extract Fine Granules at the same frequency for 6 weeks, with a 2-week washout between both administration periods (n=4).

Responders had to meet criterion (1) and one of the three other criteria (2) to (4): (1) good drug compliance; (2) subjective overall evaluation improved; (3) clinical symptoms improved; or (4) symptoms other than chief complaint improved.

**6. Main outcome measures**

36-item short-form health survey (SF36), profile of mood states (POMS), natural killer (NK) activity, interleukin (IL)-2-producing activity of peripheral lymphocytes, lymphocyte-proliferating activity, and lymphocyte cell-surface antigens.

**7. Main results**

PCS (physical component summary) of SF36 was significantly improved in the hochuekkito group ($P<0.05$). There were significant among-arm differences in 4 (anger-hostility, fatigue, tension-anxiety, confusion) of 6 subscales of the POMS ($P<0.01$, $P<0.05$, $P<0.01$, $P<0.05$, respectively). Lymphocyte cell-surface antigens, CD3-positive cells, and CD3/CD4 double-positive cells were significantly increased in the hochuekkito group ($P<0.05$).

**8. Conclusions**

Hochuekkito improves the QOL of elderly patients with weakness and activated their immune systems.

**9. From Kampo medicine perspective**

None.

**10. Safety assessment in the article**

No adverse drug reactions occurred.

**11. Abstractor's comments**

The design of this study is very interesting, being a combination of RCT and N-of-1 trial. The authors mention that 15 candidates were registered and none dropped out; however, the actual number was 13 (four participants in arm 1, five in arm 2, and four in arm 3). The authors treated the participants as one group, with a washout period separating the interventions in each arm, and proceeded on a two-group basis by converting to a hochuekkito (補中益気湯) group (17 participants), and a placebo group (nine participants). The authors argue that they added an N-of-1 trial to a small-scale RCT; however, there is no before-after comparison for the N-of-1 trial, and it rather resembles a crossover trial (DB-RCT-crossover). Interpreting results from a complex design is difficult. Hopefully the authors will further develop their approach.

**12. Abstractor and date**

Tsuruoka K, 15 June 2007, 1 April 2008, 1 June 2010, 31 December 2013.