

## 9. Cardiovascular Diseases

**Reference**

Akiyama Y, Ohno S, Asaoka T, et al. The combination therapy with sarpogrelate hydrochloride and Kampo medicine (oren-gedoku-to or toki-shakuyaku-san) for Raynaud's phenomenon. *Japanese Journal of Oriental Medicine* 2001; 51: 1101-8 (in Japanese with English abstract). CiNii

**1. Objectives**

To evaluate the effectiveness of orengekuto (黄連解毒湯) in improving peripheral circulation in Raynaud's phenomenon.

**2. Design**

Quasi-RCT.

**3. Setting**

Two departments (Department of Rheumatology and Department of Oriental Medicine) in Saitama Medical School, Japan.

**4. Participants**

Twenty patients with Raynaud's phenomenon who consulted at the above two departments between October and March from 1994 to 1997 (3 men and 17 women).

**5. Intervention**

Arm 1: oral administration of sarpogrelate hydrochloride (100mg) in three divided doses after meals.

Arm 2: oral administration of sarpogrelate hydrochloride (100mg) in three divided doses after meals, and orengekuto (黄連解毒湯) 2.5 g t.i.d. before meals.

Arm 3: oral administration of sarpogrelate hydrochloride (100 mg) in three divided doses after meals, and tokishakuyakusan (当帰芍薬散) 2.5 g t.i.d. before meals.

**6. Main outcome measures**

Raynaud's phenomenon – subjective symptoms (cold sensation, numbness, pain) and increase in skin temperature assessed by thermography (increase of more than 0.6°C in the mean temperature of all 10 fingertips of both hands) – were evaluated before and after 12-week treatment. The efficacy was compared among subjects with different “*sho*” (証, pattern) (*jitsu-sho* [実証, excess pattern], *chukan-sho* [中間証, intermediate pattern], and *kyo-sho* [虚証, deficiency pattern]) in Kampo medicine.

**7. Main results**

After 12-week treatment, the combination with orengekuto had significantly higher efficacy than sarpogrelate hydrochloride alone (90% vs. 52.5%;  $P < 0.02$ ), while the combination with tokishakuyakusan had similar efficacy to sarpogrelate hydrochloride alone. Skin temperature at the fingertips was significantly increased in arm 3 ( $1.8 \pm 1.9^\circ\text{C}$ ;  $P < 0.02$ ) compared with arm 1 ( $0.6 \pm 0.8^\circ\text{C}$ ), and also significantly elevated in arm 2 ( $4.1 \pm 2.1^\circ\text{C}$ ;  $P < 0.005$ ) compared with arm 3. Combination therapy with Kampo formulations was effective in patients with *jitsu-sho*, but not in patients with *kyo-sho*.

**8. Conclusions**

Orengekuto combined with sarpogrelate hydrochloride has higher efficacy in the treatment of Raynaud's phenomenon. However, *kyo-sho* patients did not respond to this combination therapy and had higher incidence of adverse drug reactions (ADRs), suggesting the importance of prescriptions according to the patient's “*sho*.”

**9. From Kampo medicine perspective**

In this study, 72.7% of the subjects were regarded as *kyo-sho* type. No subject was identified as the so-called orengekuto-*sho* type – having conditions that are expected to respond to orengekuto therapy. In *kyo-sho* subjects, the efficacy of the orengekuto combination therapy was similar to that of sarpogrelate hydrochloride monotherapy, and a higher dropout rate was observed because of ADRs from the bitherapy. Therefore we suggest that administration of sarpogrelate hydrochloride plus orengekuto should be withheld from *kyo-sho* subjects.

**10. Safety assessment in the article**

ADRs of the orengekuto combination occurred in *kyo-sho* patients, including nausea (n=2) and diarrhea (n=2), neither of which was serious. No serious ADRs due to the tokishakuyakusan combination were noted.

**11. Abstractor's comments**

Sarpogrelate hydrochloride in combination with orengekuto, which has been reported to improve peripheral circulation, improved more efficiently peripheral circulation in Raynaud's phenomenon when compared with sarpogrelate hydrochloride monotherapy as positive control in this study. It is interesting that improvement was greater with this combination than with the tokishakuyakusan combination, even when more than 70% of subjects were *kyo-sho*. Further scientific evaluation with a larger number of subjects is awaited.

**12. Abstractor and date**

Ushiyama T. 1 April 2008, 1 June 2010, 31 December 2013.