Kampo Medicine - Current Research

Varieties of Effects of Shakuyakukanzoto

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Shakuyakukanzoto is the formula first appeared in "Shan Han Lung". This has a simple composition comprising peony root and licorice root. Despite the simple makeup, it has powerful and potential medicinal benefits and versatile applications across therapeutic categories. *Shakuyakukanzoto* known in Japan as a magic bullet for so-called "komuragaeri (muscle cramps)" has also useful prophylactic efficacy against it. Thus, sports lovers as well as other people habitually use it. For instance, they often take it before golf competitions, going hiking, and long distance bicycle touring in order to prevent muscle fatigue in the lower extremity muscle fatigue; mothers who learn of their child having a football game give this formula to him on the night before the game. Moreover, this formula has the actions of preventing or resolving striated muscle fatigue or cramps, relieving colicky pain caused by the contraction of smooth muscles, and improving hyperprolactinemia. It is also used for preventing acne.

Varieties of effects of *shakuyakukanzoto* and the results of clinical trials will be introduced as below based on the clinical results:

1. Muscle cramps

Since it is too basic that *shakuyakukanzoto* is effective for muscle cramps, only a few reports have been published. Muscle cramps occur mostly during night. One pack (2.0 – 2.5g) dose before sleep has the preventive effect. Even after the occurrence, cramps will be relieved promptly with one pack dosing. In this chapter, a study will be introduced on the use of the formula for the patients with hepatocirrhosis who had the onset of komurogaeri (muscle cramps) when they were undergoing artificial dialysis.

Kumakura, et al. administered on demand the Extract of *shakuyakukanzoto* 2.5g to 23 hemodialytic patients (male 10, female 13, aggregated number of patients 61) immediately after they claimed the onset of muscle cramps while undergoing artificial dialysis. Muscle cramps disappeared in 54 patients (88.5%), and an average time taken to achieve the dissipation of pain was 5.4±3.9 minutes. The amount of physiological saline solution per dialysis needed for the cramp treatment was reduced to about one thirds (p<0.0001) from that before the use of *shakuyakukanzoto*[1].

Kumada, et al. divided 101 patients with the diagnosis of hepatocirrhosis who had the experience of muscle cramps twice or more during a week (four times or more during two weeks) in the positive drug group (52 patients: male 21 and female 31) and the control group (49 patients: male 26 and female 23). Extract of *shakuyakukanzoto* (7.5g/day) was administered in the positive drug group for two weeks, whereas placebo (7.5g/day) was used in the control group for two weeks. In the group of Extract of *shakuyakukanzoto*, the frequency of muscle cramp occurrence was markedly improved in 4 patients, improved in 31, remained unchanged in 14, and worsened in 3 with the overall result of improved or above in 67.3% of the patients. In the placebo group, the frequency was markedly improved in 5 patients, improved in 13, remained unchanged in 22, and worsened in 8 with the overall result of improved or above in 37.5%. The effect in the positive drug group was significantly superior (p< 0.05) to that in the placebo group. And the overall improvement rate was also higher in the positive drug group[2].

2. Dysmenorrhea

Dysmenorrhea is a syndrome associated with menstruation characterized mainly by spasm-like acute pain in the lower abdomen and backache. It has two types – functional dysmenorrhea and organic dysmenorrhea. *Shakuyakukanzoto* is used for both of them. Studies that have been reported until now are as follows:

Inoue, et al. measured effects, using a pain scale, of the Extract of *shakuyakukanzoto* in 42 patients who suffered from dysmenorrhea of moderate to severe degrees (age 14-49, average age 30.4: functional dysmennorhea-18, organic dysmenorrheal-24): the administration of the formula 2.5g/day was commenced from 5 to 7 days before the expected first date of their menstruation period and then 7.5g/day for 2-3 days after the start of menstruation, and pains were assessed by 5 pain intensity scales from extreme pain to pain free. (Pain improved by 3 scales is assessed as prominently effective; improved by 2 scales is effective; improved by not more than 1 is ineffective.) The results were that prominently effective was 31.0%, effective 57.1%, and ineffective 11.9%, and the overall effectiveness was 88.1%. There was no significant difference between the group of functional dysmenorrheal (88.9%) and the group of organic dysmenorrheal (87.5%)[3].

Ohta, et al. administered the Extract of *shakuyakukanzoto* (7.5g/day divided in 3 doses) to 25 patients with dysmenorrhea of moderate to severe degrees (age 17-37, average 25.2±5.2) for 10 days from the expected commencement date of menstruation. Pains were assessed three times using the VAS scale at the time of registration (previous menstrual pain was registered at the hospital), at the time of menstruation, and at the time of hospital visit. For 14 patients after excluding those whose pains could not appropriately be grasped, pains at the time of each month's menstruation and at the time of hospital visit were compared based on VAS values. Vas values declined and effects were sustained in 6 patients (42.9%); effects in each menstrual cycle were not consistent in 4 patients (28.6%); although VAS values declined, effects were not identifiable in 2 (14.3%); and ineffective in 2 (14.3%)[4].

References

Tanaka, et al. report that they administered the Extract of *shakuyakukanzoto* (7.5g/day divided in 3 doses) to 12 patients with functional dysmenorrheal and organic dysmenorrhea of moderate to severe degrees (age: 22-46, average 33.0±8.7, functional-4 and organic-8). The administration was commenced from 7 days before their expected first day of menstruation until the last day of their menstrual period. Subsequently, the preparation 7.5/day was continuously administered until 7 days prior to the start of their next expected menstrual cycle, resulting in prominent effects in 12 patients after three menstrual cycles[5].

3. Hypertestosteronemia and hyperprolactinemia

Recent studies have elucidated that *shakuyakukanzoto* has effects on Hypertestosteronemia and hyperprolactinemia. As a result, this preparation is believed to have applications for any disorders developed by hormonal abnormalities. Especially, there are several documents reported in the gynecologies that it was useful for the patients who complained of anovulation or infertility due to hormonal abnormalities.

Yaginuma, et al. administered the Extract of *shakuyakukanzoto* (7.5g/day) to 110 patients (anovulation 78, rare occurrence of ovulation 15, normal menstrual cycle 17) out of 128 patients with high blood levels of testosterone of 0.7ng/ml or higher (age 26.7±0.4), after excluding those who were not appropriate to have evaluations. After 16-week administration, blood levels of testosterone, estrone (E_1), estradiol, cortisol, FSH,

LH, and prolactin were compared before and after the administration. For 10 patients who showed the blood prolactin levels were 25ng/ml or above, fluctuations in its level were also reviewed. The results were that from two-week administration onward, the blood levels of testosterone and E_1 were significantly reduced ($p<0.001$, $p<0.05$ for each) and 78 patients with anovulation (42.3%) recovered the regular ovulation cycle. Moreover, the blood prolactin levels in 10 patients were significantly reduced ($p<0.05$)[7].

Takahashi, et al. administered the Extract of *shakuyakukanzoto* (7.5g/day) for 24 weeks to 34 patients of the group of polycystic ovary syndrome, who had polycystic swellings in both ovaries found on an ultrasonic examination with the blood testosterone levels of 100ng/dl and compared the levels of the testosterone before and after the administration, resulting in reduced levels in 30 patients (91%). Average testosterone levels dropped in the 4th week from the pre-administration levels of 137.1±27.6ng/dl to 85.3 ± 38.3ng/dl ($p < 0.001$). Similarly, the levels reduced in 12th week and 24th week[8].

Itoh, et al. administered the Extract of *shakuyakukanzoto* (7.5g/day) to 51 patients who visited our facility with the complaint of infertility and was diagnosed as having occulted hyperprolactinemia by a TRH test, and compared the TRH prolactin levels at 30-min time points before the administration and after 8 weeks administration. The patients who had the administration for 8 weeks or more and was able to have re-tests of TRH loading was 22, of which 16 (72.7%) showed reduced blood prolactin. Furthermore, the overall blood prolactin levels dropped significantly from 79.1±14.9ng/ml to 65.3±20.9ng/ml ($p<0.001$)[9].

It may be considered from these reports that *shakuyakukanzoto* has the action of lowering high levels of blood testosterone and blood prolactin. If *shakuyakukanzoto* is administered for those in the normal ranges, they will not be lowered more than necessary.

4. Abdominal pain

Shakuyakukanzoto is used for pain that suddenly occurs. Especially, this preparation has many applications for abdominal pain induced by spasms of smooth muscles. Case reports on the use of this preparation for biliary stones, urinary stones, and irritable bowel syndrome have been reported and reports of case series, although limited, have been submitted.

Nagata, et al. assessed the intensity of abdominal pain before and after the administration of *shakuyakukanzoto* in 45 patients (irritable bowel syndrome-29 patients, biliary dyskinesia-7, bladder stones-2, kidney stones-3, abdominal pain after taking a medicine-4): Pain intensity before the administration was classified into most serious, serious, moderate, mild and symptom-free. The results showed an effectiveness rate of 79.3% with an ineffectiveness rate of 20.7% in the irritable bowel syndrome group and an effectiveness rate of 71.4% with an ineffectiveness rate of 28.6% in the biliary dyskinesia group. In the group of bladder stones, one patient had effects while one patient did not have effects. In the group of kidney stones, two patients had effects and one patient did not have effects. In the group of abdominal pain after taking medicine, two patients had effects while two patients did not have effects[10].

For the purpose of reference

Katsura, et al. made an observation to compare effects between the two medicines of *Kanzoto* and *shakuyakukanzoto* in 130 patients who visited Pediatric Outpatients because of common cold, acute gastroenteritis or other disorders (male children-69 patients, female children-61, adults-7). Each of the group of *kanzoto* and the group of *shakuyakukanzoto* was divided into the subgroup

of internal use and the subgroup of oral use. In the *shakuyakukanzoto* group, the subgroup of internal use had an effectiveness rate of 97.5% with one patient excluded, and the subgroup of oral use had an effectiveness rate of 97.9% with one patients excluded. In the group of *shakuyakukanzoto*, all patients of the subgroup of internal use had effects and the subgroup of oral use had an effectiveness rate of 92.9 with two patients excluded. In the 4 subgroups, pains disappeared within 1-3 minutes in 50% of the patients and within 5 minutes and 30 seconds in 80%[11].

5. Acne vulgaris

Kampo medicines have an appropriate indication for acne. Reports on *seijobofuto* and *keigairengyoto* can be seen quite often. Kampo preparations are effective enough for pustular acne vulgarises. However they are less responsive. One of the causes of acne vulgaris is said to be hyperandrogenemi and there are several studies on applications of the effect of *shakuyakukanzoto* that can improve this clinical condition.

Aaizawa administered *shakuyakukanzoto* to 19 female patients with Kligman classification stage II acne vulgarises (age: 14-30, average 25) and compared improvements in the condition and changes in blood hormone levels before and after the administration. The administration period was about 2 weeks from the 7th day from the date menstruation started (mid follicular phase) to the mid follicular phase after a menstrual cycle. The results showed that the number of papules remained unchanged, the number of comedones significantly reduced, and subjective symptoms of seborrhea were markedly improved in 4 patients, moderately improved in 6, mildly improved in 5, and remained unchanged in 4. The results of clinical effect assessment were that 11 out of 19 (60%) had moderate or more improvements. Concerning blood hormone levels, testosterone (T) was significantly reduced from 37.8±13.3ng/dl before the administration to 30.7±16.2 ng/dl after the administration ($p<0.01$). Free testosterone (FT) was also lowered significantly although no significant differences were observed between before and after the administration in the levels of dehydrotestosterone, dehydroepiandosterone, dehydroepiandosterone sulfate, sex hormone binding globlin[12].

Tanaka, et al. administered *shakuyakukanzoto* to the patients with acne vulgarizes (2 males and 11 females from 16 to 32 years old) and made an assessment after 2 months. There were no patients who had hyperandrogenemia. The results were markedly effective in 1 patient, effective in 4, ineffective in 4, and drop-out 4. Significant changes in the levels of blood androgens were not observed[13].

It is clear from two studies above that *shakuyakukanzoto* is effective for acne vulgaris. Concerning blood androgens, T and FT showed high levels in some patients. However, *shakuyakukanzoto* works to lower high levels of these although it will hardly change levels that are in the normal range from the beginning. And it can be understood that the preparation works effectively for acne. It seems that the preparation does not reduce the number of papulars but reduces the number of comedones and thereby resolve acne.

6. Others

Shakuyakukanzoto is often used for spasmodic pains of smooth and skeletal muscles. In order to apply this effect, a study was conducted on analgesic potency for hemorrhoid pain.

Endo, et al. made a comparative clinical trial of the effect of ointment alone and in combination of ointment and *shakuyakukanzoto* with the subjects of 100 patients who visited the facility for

the treatment of anal fissure and non-surgical treatment was considered appropriate (male 48, female 52). Of these patients, 50 were assigned to the group of ointment alone treatment and the remaining 50 patients were assigned to the group of combination therapy of ointment and *shakuyakukanzoto*. The group of ointment alone received Tribenoside-lidocaine ointment injections into the anus twice/day and the group of the combination medication received Tribenoside-lidocaine Ointment and the Extract of *shakuyakukanzoto* 6g in 3 doses before or between meals. The administration continued at least for 17 days.

The intensity of pain was assessed by VAS scales, and the nature of pain, time, influence of pain on everyday life, the severity of hemorrhage, and the number of defecations was assessed using questionnaire sheets. The severity of pain was significantly improved after 10 days in the group of ointment alone administration, whereas it was significantly improved after 3 days. Influence on everyday life was also significantly superior in the group of combination use. There were no significant differences in the severity of hemorrhage and the number of defecations. About satisfaction after treatment, satisfied or more was 32% in the group of ointment alone and 78% in the group of combination use. About overall improvement, improved or more was 32% in the group of ointment alone and 78% in the group of combination use[14].

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