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CLINICAL STUDY

Effect of Sanhuangwuji powder, anti-rheumatic drugs, and ginger-partitioned acupoint stimulation on the treatment of rheumatoid arthritis with peptic ulcer: a randomized controlled study

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Abstract

OBjECTIVE: To observe the efficacy and safety of oral Sanhuangwuji powder, anti-rheumatic drugs (ARDs), and ginger-partitioned acupoint stimulation at Zusanli (ST 36) on the treatment of rheumatoid arthritis (RA) complicated by peptic ulcer.

METHODS: This prospective randomized controlled study included 180 eligible inpatients and outpatients randomly assigned to an ARD treatment (n = 60), ginger-partitioned stimulation (n = 60), or combination treatment (n = 60). Patients assigned to the ARD group were given oral celecoxib, methotrexate, and esomeprazole. Patients assigned to theginger-partitioned stimulation group were given ginger-partitioned acupoint stimulation at Zusanli (ST 36) in addition to the ARDs. Patients in the combination treatment group were given oral Sanhuangwuji powder,ginger-partitioned acupoint stimulation at Zusanli (ST 36), and ARDs. All patients were followed up for 2 months to evaluate clinical effects and safety. The study was registered in the World Health Organization database at the General Hospital of Chengdu Military Area Command Chinese People's Liberation Army (ChiCTR- TCC12002824).

RESULTS: The combination treatment group had significantly greater improvements in RA symptoms, laboratory outcomes, and gastrointestinal symptom scores, compared with the other groups ($P < 0.05$). The peptic ulcer healing rate in the combination treatment group was significantly greater than that in the ARD treatment group ($\chi^2 = 16.875$, $P < 0.05$) and the ginger-partitioned stimulation group ($\chi^2 = 6.171$, $P < 0.05$).

CONCLUSION: Combination treatment with ginger-partitioned acupoint stimulation at Zusanli (ST 36), oral Sanhuangwuji powder, and ARDs had a better clinical effect for RA with complicated peptic ulcer, compared with ARD treatmentalone or in combination with ginger-partitioned acupoint stimulation.

Key words: Arthritis, rheumatoid; Peptic ulcer; Point ST 36 (Zusanli); Sanhuangwuji powder; Randomized controlled trial

INTRODUCTION

Rheumatoid arthritis (RA) is a common autoimmune disorder with a worldwide incidence of 1%-2%.[1] Active RA manifests primarily as synovitis of small joints, which causes joint swelling and pain.[1] Non-selective non-steroidal anti-inflammatory drugs (NSAIDs) are frequently prescribed to alleviate arthralgia and control synovitis. However, these drugs can have serious adverse effects, especially on the gastrointestinal (GI) tract, and are likely to induce peptic ulcers. Thomas *et al* [2] used endoscopy to follow up patients with RA who were medicated with non-selective NSAIDs for 3 consecutive months, and found that approximately 25% of patients suffered from peptic ulcers, with a three-fold increase in morbidity rate.[3] Matsukawa *et al* [4] reported that the incidence of gastric ulceration was 80.6% in patients with RA medicated with aspirin. The adverse effects of non-selective NSAIDs are believed to be associated with cyclooxygenase (COX)-1 inhibition. Therefore, NSAIDs that selectively inhibit COX-2 (coxibs) have been developed, and are effective for alleviating synovitis with minimal adverse GI effects. Nevertheless, Raymond *et al*[5] reported that the frequency of GI injury, erosion, or ulceration was 21.4% after 12 weeks in RA patients given celecoxib, a COX-2 inhibitor.

Recently published studies have focused on the prophylaxis of NSAID-induced ulcers. Combination treatment with a proton pump inhibitor and an NSAID significantly decreases the risk of peptic ulceration in patients with RA.[6] Höer *et al* [7] found that concomitant prescription of a proton pump inhibitor with diclofenac reduced the odds ratios of ulcer-associated hospitalization from 2.4 to 1.3. Wayne *et al* [8] suggested that co-administration of a proton pump inhibitor with an NSAID was as effective as a coxib at reducing NSAID-induced gastropathy risk. Similarly, García-Rodríguez *et al*[9]reported that coxibs conferred a lower risk of serious upper GI complications than NSAIDs, and the addition of gastroprotective co-therapy reduced the NSAID-associated risk by nearly 40%. Chan *et al* [10] noted that patients taking celecoxib with esomeprazole, but not low-dose aspirin, had a lower risk of recurrent peptic ulcer bleeding than patients treated with celecoxib alone.

The treatment of RA complicated by peptic ulcer is challenging, and no standardized protocol exists in clinical practice. A conventional RA treatment regimen will not be effective in this scenario because the use of NSAIDs, including COX-2 inhibitors, or corticosteroids is limited in patients with gastric ulcers or concomitant gastric and duodenal ulcers.

Moxibustion is an important technique within Traditional Chinese Medicine, and stimulating the Zusanli (ST 36) acupoint has been shown to be effective for treating RA. We aimed to investigate the clinical effect and safety of oral Sanhuangwuji powder, used in combination withZusanli (ST 36) acupoint stimulation andanti-rheumatic drugs for the treatment of active RA complicated by peptic ulcer.

MATERIALS AND METHODS

Patients

Patients aged 45-65 years with RA and peptic ulcer disease were included in the trial. Sample size was determined according to the clinical test 1∶1 control, 20% surplus principle, and parallel design number estimation table. Two hundred patients were initially enrolled. Ten patients did not meet the inclusion criteria for after further screening, and six patients declined to participate, still four patients who had other reasons were excluded. In total, 180 inpatients or outpatients with RA and complicated peptic ulcer were prospectively and consecutively enrolled at the Traditional and Western Medicine Department of Rheumatology, PLA Chengdu General Hospital China between July 2008 and July 2013. Patients were equally and randomly assigned to three treatment groupsby random number table (Figure 1). The study wasregistered in the World Health Organization database at the General Hospital of Chengdu Military Area Command Chinese People's Liberation Army (ChiCTR-TCC12002824), and was approved by the hospital's ethics committee and institutional review board. All participants gave a written informed consent before inclusion.

Diagnosis and syndrome differentiation of RA

RA was diagnosed in accordance with the revised criteria for RA classification established by the American Rheumatism Association in 1987.[11] Active disease was defined as an aggravated joint swelling and pain, increased erythrocyte sedimentation rate (ESR), and elevated C-reactive protein (CRP). Traditional Chinese Medicine (TCM) syndrome differentiation of RA was performed in accordance with the Guidelines for Clinical Study of Traditional Chinese Medicine New Drugs.[12]

Inclusion criteria

Patients were included if they had: active RA and a TCM syndrome differentiation of arthralgia (aggravated arthralgia with a concomitant syndrome of dampness and heat blocking collaterals); were aged 45-65 years; and had a diagnosis of complicated peptic ulcer confirmed by endoscopy. Patients must not have had previous treatment for RA and peptic ulcer using TCM or Western drugs. Patients must give written and informed consent before enrollment.

Exclusion criteria

Patients were excluded from this study if they had: allergies to any test medications; complicated Helicobacter pylori infection, GI cancer, or GI bleeding; any other autoimmune disorders; serious concomitant cardiac, cerebral, hepatic, renal, hematological, or endo-

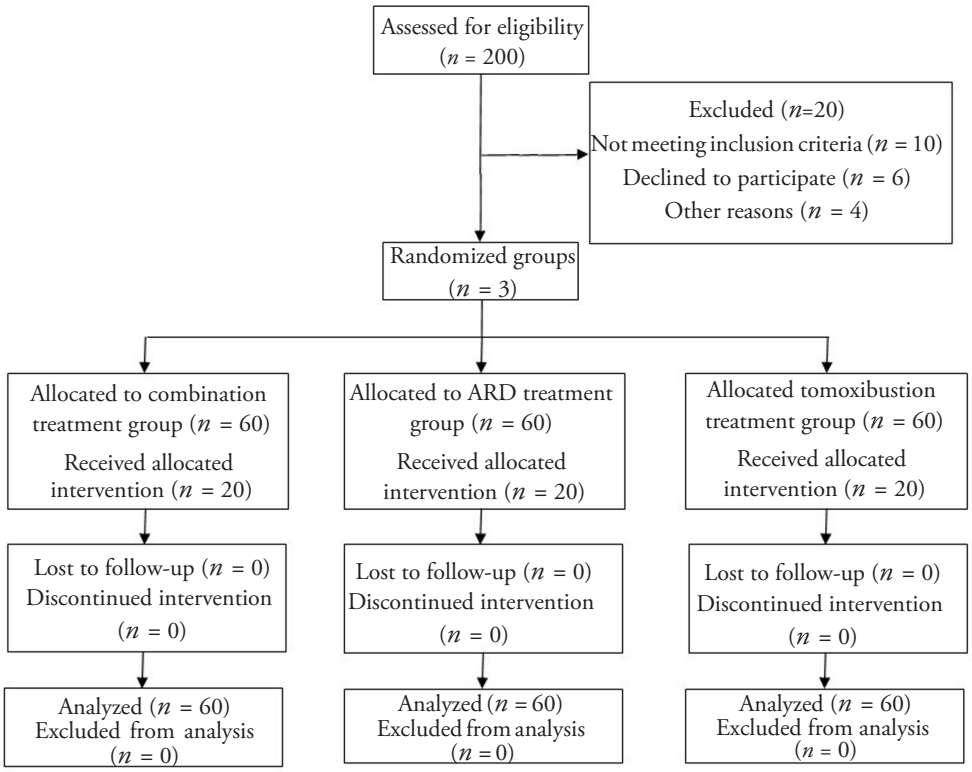

Figure1 Flow chart of participation in this study

crine disorders; or impaired consciousness or psychiatric disorders. Patients were also excluded if they participated in any other clinical studies within the previous 3 months, or for any other reasons at the discretion of the investigators. Pregnant or lactating women were also excluded.

Treatments

ARD treatment. Patients were given 20-mg oral esomeprazole magnesium enteric-coated tablets (Astra Zeneca, London, UK) once daily, 5 min before breakfast; 100-mg oral celecoxib capsules (Pfizer, New York, NY, USA) twice daily; and 15-mg oral methotrexate tablets (Sine Pharmaceutical Co., Ltd., Shanghai, China) once weekly.

Ginger-partitioned stimulationof the Zusanli (ST 36) acupoint. Patients were administered ARD treatment and ginger-partitioned stimulation at Zusanli (ST 36). A 5-mm-thick fresh ginger slice was placed over Zusanli (ST 36) and the point was stimulated with the endurable heat from a burning moxa-stick for 10-15 min. Moxibustion was performed twice daily.

Combination treatment. Patients were administered ARD treatment, moxibustion, and oral Sanhuangwuji powder (10 g per dose, three times a day). Sanhuangwuji powder was prepared by PLA Chengdu General Hospital Pharmacy, and contained Huangqin (*Radix Scutellariae Baicalensis*) 15 g, Huanglian (*Rhizoma Coptidis*) 10 g, Huangbai (*Cortex Phellodendri Amurensis*) 15 g, Dilong (*Pheretima Aspergillum*) 10 g, Haipiaoxiao (*Endoconcha Sepiellae*) 30 g, and Baiji (*Rhizoma Bletillae Striatae*) 15 g. This powder was taken alone, and the patients were instructed to avoid any raw, cold, spicy, or tough foods, and alcohol during the treatment. One treatment cycle lasted 4 weeks, and a follow-up fiber-optic endoscopy was repeated after two cycles of treatment.

Outcome measures

Outcome measures included the number of swollen joints, the number of tender joints, the duration of morning stiffness, gripping strength, self-reported pain score, DAS-28 RA disease activity score, a health assessment questionnaire (HAQ) for quality of life, levels of serum rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP), ESR, and CRP. These were assessed at the baseline, and 4 and 8 weeks after treatment. Any GI symptoms, such as abdominal pain, reflux, belching, and abdominal distension, were documented and semi-quantitatively scored. A GI endoscopy was performed at baseline and 8 weeks after treatment.

Evaluation of RA treatment efficacy

RA treatment efficacy outcomes were classified based on ACR20, ACR50, and ACR70 improvement criteria, as established by the American College of Rheumatology.[13] Briefly, ACR20 refers to a 20% improvement in the number of tender and swollen joints and more than a 50% reduction in scores for at least three items out of: the pain visual analog scale (VAS), the patient-reported symptom score, the physician-reported symptom score, the HAQ, and RF, ESR, or CRP levels. ACR50 and ACR70 respectively refer to 50% and 70% improvements in the same metrics as ACR20. RA treatment outcome was determined to be significantly effective if ACR70 was achieved (primary symptoms,

signs, RF, ESR, and CRP improved, with an overall improvement in the score of > 70%); moderately effective if ACR50 was achieved (primary symptoms, signs, RF, ESR and CRP improved, with an overall improvement in the score of 20%-70%); or ineffective if ACR20 was not achieved (primary symptoms, signs, RF, ESR and CRP improved, with an overall improvement in the score of < 20%). The primary symptoms and signs included the number of swollen joints, the number of tender joints, the duration of morning stiffness, the average gripping strength, and the pain VAS. The improvement rate was defined as the mean of the improvement percentages [(pre-treatment score – post-treatment score)/pre-treatment score × 100%] for the five outcome measures.

Evaluation of peptic ulcer treatment effect

All patients were followed up at 4 weeks and 8 weeks to assess the GI symptom score and the clinical efficacy of peptic ulcer treatment.[14] Peptic ulcer treatment outcome was determined to be ineffective if the reduction in ulcer area was < 50%, with aggravation of abdominal pain and symptoms of abdominal irritability; moderately effective if the reduction in ulcer area was > 50%, with the disappearance of abdominal pain and symptoms of abdominal irritability; or significantly effective if the ulcer, abdominal pain, and symptoms of abdominal irritability disappeared, with all laboratory parameters returning to normal. The overall rate of treatment success was defined as the percentage of patients exhibiting moderately or significantly effective treatment outcomes. The GI symptom score was semi-quantitatively graded as follows: 0 points, no GI symptoms; 1 point, mild symptoms requiring no medication; 2 points, moderate symptoms with slight impairment in daily life; and 3 points, severe symptoms requiring medication, with serious impairment in daily life.

Evaluation of endoscopic peptic ulcer treatment efficacy

The efficacy of peptic ulcer treatmentby endoscopy was assessed as previously described.[15] Peptic ulcer treatment outcome was determined to be: clinically cured if the ulcer completely disappeared, and there was no obvious edema; significantly effective if the ulcer disappeared, but there was still obvious inflammation; moderately effective if the reduction in ulcer area was > 50%; or ineffective if the reduction in ulcer area was < 50%.

Statistical analysis

SPSS 12.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. All continuous data are expressed as the mean ± standard deviation ($\bar{x} \pm s$), and were compared using analysis of variance followed by the least significant difference test. All categorical data were compared using a multiple, independent samples non-parametric test. A *P*-value < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

The combination treatment group (n = 60) included 14 men and 46 women with a mean age of (56 ± 6) years (range 45-65 years), and a mean RA history of (9 ± 5) years (range 2-20 years). The ARD treatment group (n = 60) included 12 men and 48 women aged (56 ±6) years (range 45-65 years), and a mean RA history of (9 ± 6) years (range 1.5-21 years). The ginger-partitioned stimulation group (n = 60) included 13 men and 47 women aged (56 ± 6) years (range 45-65 years), with a mean RA history of (9 ± 6) years (range 2.5-22 years). The three groups were comparable in terms of sex, age, and history of RA (P > 0.05).

Clinical efficacy of RA treatment

The clinical efficacy outcomes for the treatment of RA are shown in Table 1. At baseline, all groups were comparable in terms of the number of swollen joints, number of tender joints, duration of morning stiffness, pain VAS, HAQ score, and DAS-28 score (P > 0.05). Compared with the baseline measurements, significant improvements in the primary symptoms and signs were observed in all groups 4 and 8 weeks after treatment (P < 0.05). The combination treatment group had a significantly greater improvement, compared with the ARD group (P < 0.05) and the ginger-partitioned stimulation group (P < 0.05).

Laboratory efficacy of RA treatment

The laboratory efficacy outcomes for RA treatment are shown in Table 2. At baseline, all groups were comparable with regard to platelet count, ESR, serum CRP level, serum RF level, and anti-CCP titer (P > 0.05). Compared with baseline values, laboratory parameters improved significantly in the combination treatment group 4 and 8 weeks after treatment (P < 0.05). Fourweeks after treatment, the ARD treatment group exhibited significant improvements in platelet count, ESR, and serum CRP level (P < 0.05), but no significant changes in serum RF level or anti-CCP titer (P > 0.05). Four weeks after treatment, there was a significant improvement in platelet count, ESR, serum CRP level, and serum RF level in the ginger-partitioned stimulation group (P < 0.05), but no significant alteration in the anti-CCP titer (P > 0.05) compared with the baseline. These three treatment groups showed significant improvements in platelet count, ESR, serum CRP level, serum RF level, and anti-CCP titer 8 weeks after treatment (P < 0.05), relative to the baseline. Eight weeks after treatment, the combination treatment group had a significantly greater improvement in all parameters compared with the ARD treatment group (P < 0.05).

Table 1 RA-associated symptoms and signs ($\bar{x} \pm s$)

Group	*n*	Time point (week)	Number of swollen joints	Number of tender joints	Duration of morning stiffness (min)	Pain VAS	HAQ	DAS-28
Combination treatment	60	0	13.9±4.6	16.2±4.3	196.7±45.8	7.9±1.3	17.8±2.7	7.3±1.4
		4	4.9±1.3[ab]	9.0±2.7[a]	124.3±20.6[a]	3.4±1.1[ab]	8.4±1.8[ab]	3.2±1.2[ab]
		8	1.9±1.2[ab]	3.2±1.9[ab]	53.3±27.9[ab]	1.5±0.8[ab]	3.3±1.5[ab]	1.3±0.6[ab]
ARD treatment	60	0	13.8±4.5	16.0±4.5	197.3±51.1	7.8±1.2	17.6±2.9	7.0±1.5
		4	7.1±2.6[a]	10.1±3.1[a]	146.7±30.4[a]	5.2±1.3[a]	11.5±2.3[a]	5.6±1.7[a]
		8	4.8±0.7[a]	6.6±1.3[a]	89.8±26.6[a]	3.5±1.2[a]	6.6±1.7[a]	3.7±1.1[a]
Moxibustion treatment	60	0	13.8±4.7	16.1±4.4	196.9±47.9	7.9±1.4	17.7±3.1	7.2±1.6
		4	5.5±1.6[a]	8.3±2.1[a]	136.7±27.7[a]	4.0±1.5[a]	8.0±1.9[a]	4.3± .5[a]
		8	2.7±1.0[a]	4.8±1.3[a]	67.8±23.7[a]	2.3±1.3[a]	4.6±1.7[a]	2.5±0.9[a]

Notes: ARD treatment group: patients were treated with 20-mg oral esomeprazole magnesium enteric-coated tablets once daily, 100-mg oral celecoxib capsules twice daily,and 15-mg oral methotrexate tablets once weekly. Moxibustiontreatment group: patients were administered ARD treatment plus ginger-partitioned moxibustion at Zusanli (ST 36). Combination treatment group: patients were administered ARD treatment, moxibustion, and oral Sanhuangwuji powder (10 g per dose, three times a day). All treatments lasted 8 weeks. ARD: anti-rheumatic drug; VAS: visual analog scale; HAQ: health assessment questionnaire; DAS: disease activity score. [a]$P < 0.05$ for intragroup comparison; [b]$P < 0.05$ for intergroup comparison.

Table 2 RA-associated laboratory parameters ($\bar{x} \pm s$)

Group	*n*	Time point (week)	Platelets ($10^{\wedge 9}$/L)	ESR (mm/h)	CRP9 (mg/L)	RF (IU/mL)	Anti-CCP (RU/mL)
Combination treatment	60	0	389±71	99±29	78±41	576±421	285±178
		4	305±58[ab]	41±17[ab]	23±18[ab]	320±286[ab]	132±139[ab]
		8	188±70[ab]	22±12[ab]	11±7[ab]	179±101[ab]	78±43[ab]
ARD treatment	60	0	379±71	97±29	74±41	571±412	280±180
		4	346±61	66±28[a]	48±21[a]	526±388	221±141
		8	276±62[a]	42±26[a]	28±12[a]	325±200[a]	106±70[a]
Moxibustion treatment	60	0	379±71	97±29	74±41	571±412	280±180
		4	320±46[a]	61±24[a]	35±20[a]	477±264[a]	201±121
		8	256±72[a]	34±16[a]	20±14[a]	308±180[a]	98±42[a]

Notes: ARD treatment group: patients were given 20-mg oral esomeprazole magnesium enteric-coated tablets once daily, 100-mg oral celecoxib capsulestwice daily, and 15-mg oral methotrexate tablets once weekly. Moxibustion treatment group: patients were administered ARD treatment plus ginger-partitioned moxibustion at Zusanli (ST 36). Combination treatment group: patients were administered ARD treatment, moxibustion, and oral Sanhuangwuji powder (10 g per dose, three times a day). All treatments lasted 8 weeks. ARD: anti-rheumatic drug; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; RF: rheumatoid factor. [a]$P < 0.05$ for intragroup comparison; [b]$P < 0.05$ for intergroup comparison.

GI symptoms

GI symptom scores are shown in Table 3. At baseline, the three groups were comparable in terms of GI symptom score ($P > 0.05$). Compared with the baseline value, the GI symptom score in the combination treatment group was significantly higher 4 and 8 weeks after treatment ($P < 0.05$). Compared with the baseline, the ARD treatment group exhibited no significant improvement ($P > 0.05$) in GI symptom scores 4 weeks after treatment, while the ginger-partitioned stimulation group had a significant improvement 4 and 8 weeks after treatment ($P < 0.05$). The combination treatment group had a significantly greater improvement than that of the ARD treatment and ginger-partitioned stimulation groups 8 weeks after treatment ($P < 0.05$).

Clinical efficacy of peptic ulcer treatment

The clinical outcomes for the treatment of peptic ulcer are shown in Table 4. The overall success rate was 95% in the combination treatment group after two cycles of treatment. This rate was significantly higher than that in the ARD treatment group ($\chi^2 = 16.875$, $P < 0.05$), and the ginger-partitioned stimulation group ($\chi^2 = 6.171$, $P < 0.05$).

Efficacy of endoscopic peptic ulcer treatment

The effect outcomes of endoscopic peptic ulcer are shown in Table 5. The overall success rate was 96.7% in the combination treatment group after two cycles of treatment. This rate was significantly higher than that in the ARD treatment group ($\chi^2 = 16.875$, $P < 0.05$), and the ginger-partitioned stimulation treatment group ($\chi^2 = 6.171$, $P < 0.05$).

Table 3 Gastrointestinal symptom scores ($\bar{x} \pm s$)

Group	*n*	Time point (week)	Abdominal pain	Reflux	Belching	Abdominal distension
Combination treatment	60	0	2.1±0.6	2.3±0.5	2.1±0.4	2.2±0.7
		4	1.1±0.7[ab]	1.1±0.6[ab]	1.0±0.6[ab]	1.2±0.6[ab]
		8	0.3±0.4[ab]	0.4±0.5[ab]	0.5±0.5[ab]	0.6±0.5[ab]
ARD treatment	60	0	2.1±0.6	2.3±0.6	2.1±0.4	2.2±0.7
		4	1.7±0.5	1.9±0.4	1.8±0.6	1.8±0.4
		8	0.7±0.5[a]	0.9±0.8[a]	1.0±0.6[a]	1.1±0.7[a]
Moxibustion treatment	60	0	2.1±0.6	2.3±0.6	2.1±0.4	2.2±0.7
		4	1.4±0.6[a]	1.6±0.4[a]	1.4±0.7[a]	1.5±0.5[a]
		8	0.5±0.5[a]	0.6±0.4[a]	0.7±0.6[a]	0.9±0.5[a]

Notes: ARD treatment group: patients were given 20-mg oral esomeprazole magnesium enteric-coated tablets once daily, 100-mg oral celecoxib capsules twice daily, and 15-mg oral methotrexate tablets once weekly. Moxibustion treatment group: patients were administered ARD treatment plus ginger-partitioned moxibustion at Zusanli (ST 36). Combination treatment group: patients were administered ARD treatment, moxibustion, and oral Sanhuangwuji powder (10 g per dose, three times a day). All treatments lasted 8 weeks. ARD: anti-rheumatic drug. [a]$P < 0.05$ for intragroup comparison; [b]$P < 0.05$ for intergroup comparison.

Table 4 Clinical efficacy outcomes for peptic ulcer [(*n*)%]

Group	*n*	Significantly effective	Moderately effective	Ineffective	Overall success
Combination treatment	60	48 (80)	9 (15)	3 (5)	19 (95)
ARD treatment	60	36 (60)	3 (5)	21 (35)	13 (65)
Moxibustion treatment	60	42 (70)	6 (10)	12 (20)	16 (80)

Notes: ARD treatment group: patients were given 20-mg oral esomeprazole magnesium enteric-coated tablets once daily, 100-mg oral celecoxib capsules twice daily, and 15-mg oral methotrexate tablets once weekly. Moxibustion treatment group: patients were administered ARD treatment plus ginger-partitioned moxibustion at Zusanli (ST 36). Combination treatment group: patients were administered ARD treatment, moxibustion, and oral Sanhuangwuji powder (10 g per dose, three times a day). All treatments lasted 8 weeks. ARD: anti-rheumatic drug.

Table 5 Endoscopic efficacy outcomes for peptic ulcer [(*n*)%]

Group	*n*	Clinical cure	Significantly effective	Moderately effective	ineffective	Overall success
Combination treatment	60	44 (73.3)	10 (16.7)	4 (6.7)	2 (3.3)	96.7
ARD treatment	60	24 (40)	6 (10)	10 (16.7)	20 (33.3)	66.7
Moxibustion treatment	60	30 (50)	7 (11.7)	11 (18.3)	12 (20)	80.0

Notes: ARD treatment group: patients were given 20-mg oral esomeprazole magnesium enteric-coated tablets once daily, 100-mg oral celecoxib capsules twice daily, and 15-mg oral methotrexate tablets once weekly. Moxibustion treatment group: patients were administered ARD treatment plus ginger-partitioned moxibustion at Zusanli (ST 36). Combination treatment group: patients were administered ARD treatment, moxibustion, and oral Sanhuangwuji powder (10 g per dose, three times a day). All treatments lasted 8 weeks. ARD: anti-rheumatic drug.

DISCUSSION

In TCM, RA is classified as arthralgia or gout, and manifests primarily as joint swelling, burning sensations, and pain. RA is also normally diagnosed asaccumulated dampness-heat. A dampness-heat disorder is thought to result from chronic refractory *Yin-Yang* disharmony and dampness-heat crosslinking, which leads to joint swelling, burning pain, numbness, and paralysis.

Moxibustion is a TCM modality often used for prophylaxis and treatment. The technique acts directly on the disease site, which promotes analgesic and anti-inflammatory effects. Moxibustion is cheap, easy to use, and has few adverse effects. Zusanli (ST 36), an acupoint on the stomach channel, is preferred for the treatment of GI disorders in accordance with combination treatment theory for visceral disorders. Stimulating Zusanli (ST 36) is believed to invigorate the spleen and stomach, and regulate *Qi* flow for pain relief. Warming acupuncture can bidirectionally regulate disease *via* the meridians,[15] and warming acupuncture at the Zusanli (ST 36) acupoint has been reported to reduce aspirin-induced adverse GI effects.[16] The combination of warming acupuncture and ARD was shown to improve RA treatment efficacy and minimize the adverse effects of NSAIDs.[17] Li *et al*[18,19]reported that partitioned moxibustion combined with methotrexate suppressed serum interleukin (IL)-1β, tumor necrosis factor (TNF)-α,

and soluble IL-2 receptor levels, improved metatarsal joint swelling, and enhanced methotrexate treatment efficacy in RA rats. Ouyang *et al* [20] found that electroacupuncture on patients with RA could increase TNF-α and VEGF levels in the peripheral blood and joint synovia, which was clinically effective for RA treatment. Acupuncture can also relieve a wide range of pain syndromes, such as neck disorders, tension-type headaches, peripheral joint osteoarthritis, RA, shoulder pain, and lower back pain.

Sanhuangwuji power consists of Huangqin (*Radix Scutellariae Baicalensis*), Huanglian (*Rhizoma Coptidis*), Huangbai (*Cortex Phellodendri Amurensis*), and Dilong (*Pheretima Aspergillum*), with Haipiaoxiao (*Endoconcha Sepiellae*), and Baiji (*Rhizoma Bletillae Striatae*). Baicalein, a compound extracted from Huangqin (*Radix Scutellariae Baicalensis*), can inhibit the production of inflammatory cytokines by suppressing the activation of the transcription factor, nuclear factor-kappa light-chain enhancer of activated B cells, and the phosphorylation of nuclear factor of kappa light-polypeptide gene enhancer in B-cell inhibitors, alpha. Baicalein can also arrest the degranulation of mast cells.[21] Berberine, a common compound found in Huanglian (*Rhizoma Coptidis*) and Huangbai (*Cortex Phellodendri Amurensis*), can improve synovitis and inhibit the specific immune response in mice with collagen-induced arthritis, by suppressing the secretion of interferon-γ, IL-17, IL-2, and IL-10.[22] Dilong (*Pheretima Aspergillum*) significantly inhibits histamine-induced mouse hind paw swelling, rosin-induced inflammatory granuloma formation, and yeast-induced fever.[23] In our previous study, Sanhuangyilong decoction which mainly included Huangqin (*Radix Scutellariae Baicalensis*), Huanglian (*Rhizoma Coptidis*), Huangbai (*Cortex Phellodendri Amurensis*), Dilong (*Pheretima Aspergillum*), and Fuling (*Poria cocos*), could improve synovitis and immunity, and was effective significantly faster than NSAIDs.[24] Haipiaoxiao (*Endoconcha Sepiellae*), and Baiji (*Rhizoma Bletillae Striatae*) have potent anti-acid, hemostatic, and analgesic effects, and are often used for the treatment of peptic ulcer.[25,26]

In conclusion, oral Sanhuangwuji powder, in combination with ginger-partitioned stimulation at the Zusanli (ST 36) acupoint, a proton pump inhibitor, a COX-2 inhibitor, and a disease-modifying ARD, is an effective treatment for patients with RA complicated by peptic ulcer.

REFERENCE

1 **Lee DM**, Weinblatt ME. Rheumatoid arthritis. Lancet 2001; 358(9285): 903-911.

2 **Thomas J**, Straus WL, Bloom BS. Over-the-counter nonsteroidal anti-inflammatory drugs and risk of gastrointestinal symptoms. Am J Gastroenterol 2002; 97(9): 2215-2219.

3 **Steen K**, Lems W, Aertsen J, Bezemer D, Dijkmans B. Incidence of clinically manifest ulcers and their complications in patients with rheumatoid arthritis. Ann Rheum Dis 2001; 60(5): 443-447.

4 **Matsukawa Y**, Aoki M, Nishinarita S, et al. Prevalence of Helicobacter pylori in NSAID users with gastric ulcer. Rheumatology 2003; 42(8): 947-950.

5 **Cheung R**, Cheng TT, Dong Y, et al. Incidence of gastroduodenal ulcers during treatment with celecoxib or diclofenac: pooled results from three 12-week trials in Chinese patients with osteoarthritis or rheumatoid arthritis. Int J Rheum Dis 2010; 13(3): 151-157.

6 **Sugano K**, Kontani T, Katsuo S, et al. Lansoprazole for secondary prevention of gastric or duodenal ulcers associated with long-term non-steroidal anti-inflammatory drug (NSAID) therapy: results of a prospective, multicenter, double-blind, randomized, double-dummy, active-controlled trial. J Gastroenterol 2012; 47(5): 540-552.

7 **Höer A**, Gothe H, Schiffhorst G, Sterzel A, Grass U, Häussler B. Comparison of the effects of diclofenac or other non-steroidal anti-inflammatory drugs (NSAIDs) and diclofenac or other NSAIDs in combination with proton pump inhibitors (PPI) on hospitalisation due to peptic ulcer disease. Pharmacoepidemiol Drug Saf 2007; 16(8): 854-858.

8 **Ray WA**, Chung CP, Stein CM, et al. Risk of peptic ulcer hospitalizations in users of NSAIDs with gastroprotective cotherapy versus coxibs. Gastroenterology 2007; 133(3): 790-798.

9 **Rodríguez LAG**, Tolosa LB. Risk of upper gastrointestinal complications among users of traditional NSAIDs and COXIBs in the general population. Gastroenterology 2007; 132(2): 498-506.

10 **Chan FK**, Wong VW, Suen BY, et al. Combination of a cyclo-oxygenase-2 inhibitor and a proton-pump inhibitor for prevention of recurrent ulcer bleeding in patients at very high risk: a double-blind, randomised trial. Lancet 2007; 369(9573): 1621-1626.

11 **Arnett FC**, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988; 31(3): 315-324.

12 **Zheng XY**. The Guidelines for Clinical Study of Traditional Chinese Medicine New Drugs. Beijing: China Medical Science Press, 2002: 23-27.

13 **Felson DT**, Anderson JJ, Boers M, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. Arthritis Rheum 1993; 36(6): 729-740.

14 **Isomoto H**, Moss J, Hirayama T. Pleiotropic actions of Helicobacter pylori vacuolating cytotoxin, VacA. Tohoku J Exp Med 2010; 220(1): 3-14.

15 **Xiang O**, Hong Y. Immunoregulation of acupuncture and moxibustion on wind-stroke. Zhen Ci Yan Jiu 2005; 30(2): 125-128.

16 **Sun S**, Sun Z, Liu M, Li C, He W, Gao T. Warm-needle moxibustion therapy may reduce aspirin-induced gastric mucosal injury in rats. Zhen Ci Yan Jiu 2011; 36(5): 28-31.

17 **Li J**, Liu J, Ma Z, et al. Clinical observation on treatment of rheumatoid arthritis with cake-separated mild moxibustion combined with Western Medicine. Zhong Yi Zhen Jiu Xue 2006; 26(3): 192-194.

18 **Li JW**, Liu JM. Effects of partitioned warm moxibustion combined with methotrexate on RA mouse joint swelling and sIL-2R. Zhong Guo Yi Yao Zhi Nan 2008; 6(23): 355-356.

19 **Li JW**, Liu JM. Effects of partitioned warm moxibustion combined with methotrexate on RA mouse joint swelling, IL-1β, and TNF-α. Shanghai Zhen Jiu Za Zhi 2008; 27 (11): 32-34.

20 **Ouyang BS**, Gao J, Che JL, et al. Effect of electro-acupuncture on tumor necrosis factor-α and vascular endothelial growth factor in peripheral blood and joint synovia of patients with rheumatoid arthritis. Chin J Integr Med 2011; 17(7): 505-509.

21 **Lee MS**, Ernst E. Acupuncture for pain: an overview of Cochrane reviews. Chin J Integr Med 2011; 17(3): 187-189.

22 **Hu Z**, Jiao Q, Ding J, et al. Berberine induces dendritic cell apoptosis and has therapeutic potential for rheumatoid arthritis. Arthritis Rheum 2011; 63(4): 949-959.

23 **Balamurugan M**, Parthasarathi K, Cooper EL, Ranganathan LS. Anti-inflammatory and anti-pyretic activities of earthworm extract-Lampito mauritii (Kinberg). J Ethnopharmacol 2009; 121(2): 330-332.

24 **Liu DF**, Guo MY, Zhang J, et al. Treatment of active rheumatoid arthritis by Sanhuangyilong decoction. Zhong Guo Zhong Xi Yi Jie He Za Zhi 2008; 28(8): 743-746.

25 **Yang XY**, Jia FX. The comprehensive function of Wuzeigu. Zhong Guo Hai Yang Yao Wu Za Zhi 1999; (2): 46-48.

26 **Pan ZB**.Chronic gastritis, ulcer disease and eczema rhagadiforme can treated with Baiji. Zhong Yi Za Zhi 1997; 38 (8): 453-454.