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Research paper

Efficacy of compound Qingre Granules on inflammatory markers in patients with fever of unknown origin: A randomized clinical trial

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ABSTRACT

Introduction: Inflammatory-marker profiles in patients with fever of unknown origin (FUO) are largely unclear. Qingre Granules (QRG) have been used to treat patients with FUO. The aim of this study was to investigate the inflammatory-marker levels in patients with FUO, and assess the efficacy of QRG.
Methods: Using a random numbers table FUO patients were assigned to one of two groups (QRG or Control). All patients were treated according to western medicine, but patients in the QRG group additionally received QRG.
Results: Treatment success rate in QRG and control group was 95.45% and 72.92%, respectively. The time period for restoration of normal body temperature in the QRG group (7.77 ± 6.35 days) was shorter than that in the control group (8.31 ± 6.81 days); however, the difference was not statistically significant ($P > 0.05$). A decrease in the levels of TREM-1, TLR4, C-reactive protein (CRP), TNF-α was observed in both groups. However, the decrease in TREM-1 and TNF-α levels in the QRG group was much greater than that in the control group ($P < 0.05$). Moreover, TREM-1 positively correlated with the levels of IL-10 and TNF-α ($P < 0.05$).
Conclusions: QRG appears to be a potential therapeutic agent for patients with FUO and excessive heat syndrome, which possibly acts by reducing the levels of inflammatory markers.

1. Introduction

Despite the advances in rapid laboratory tests and diagnostic equipment, the management of fevers of unknown origin (FUO) can be challenging. The proportion of undiagnosed cases has varied between 9.7% and 28.9% in recent studies [1,2]. Traditional Chinese medicine (TCM) may have extensive application in the management and differential diagnosis of FUO. However, the construction of algorithms covering all possible causes of FUO is difficult [3]. Serum levels of inflammatory factors have been shown to positively correlate with bacteremic state among patients with sepsis, and are potentially useful biomarkers of infectious states in clinical settings [4]. However, the precise role of these inflammatory factors in the diagnosis and management of FUO is yet to be determined.

The active ingredients in Compound Qingre Granules (QRG) such as Astragalus, Rhubarb, Dandelion and Patrinia, are known to be useful for detoxification and purgation. Further, QRG has been successfully used in patients with excessive heat syndrome [5–7]. In this study, the serum levels of IL-10, tumor necrosis factor-α (TNF-α), triggering receptor expressed on myeloid cells-1 (TREM-1) and Toll-like receptor 4 (TLR4) from the patients were determined before and after treatment. Further, the underlying mechanism of the heat-clearing effect of QRG in FUO patients has been discussed.

2. Methods

2.1. Patients

A total of 96 cases with a fever of unknown origin who were treated at the Beijing Friendship Hospital (Beijing, China) between September 2013 and February 2015 were enrolled into the study. According to the inclusion criteria (patients who had fever lasting >2 weeks; or patients with temperature ≥38.5 °C, and, who met the diagnostic criteria of excessive heat syndrome), 70 cases were finally included in this study. Patients were randomly allocated to one of two groups (QRG [N = 22] and Control [48]) using a random number table. Patients in both groups were treated as per the

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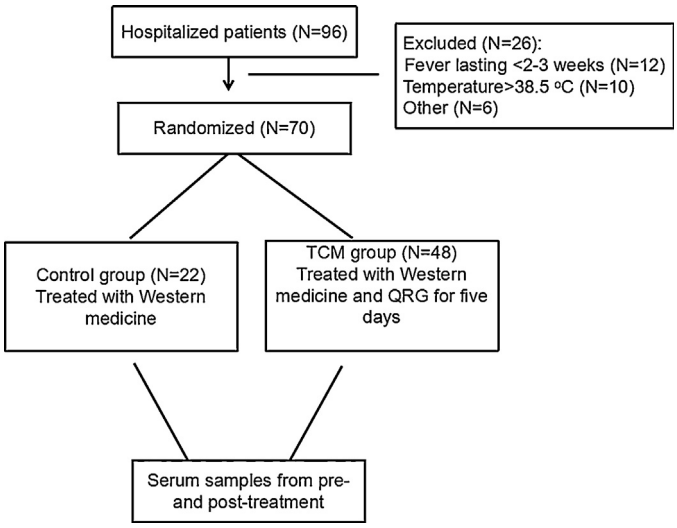

Fig. 1. Consort flow diagram.

routine protocol for FUO in western medicine. Patients in the QRG group additionally received QRG treatment. Schematic illustration of the study design and patient selection criteria were listed in Fig. 1.

Pre and post-treatment blood samples were collected from all patients. Patients who did not complete the 5-day QRG treatment were excluded from the study. The study was approved by the ethics committee at the Capital Medical University. Written informed consent was obtained from all study subjects.

2.2. Diagnostic criteria

Fever of unknown origin was defined as described elsewhere [8], i.e., patients with fever lasting >3 weeks, with temperature >38.3 °C, in whom the cause of fever remained uncertain after 1 week in hospital.

Excessive heat syndrome was defined as the presence of any of the following conditions: fever, polydipsia, abdominal distension and dry stool, red tongue with yellowish fur, full and rapid pulse or slippery pulse; increased or reduced leukocyte count.

2.3. Treatment

Compound Qingre Granules (QRG) are composed of 30 g Astragalus (Astragalus membranaceus (Fisch.) Bunge.), 3 g Rhubarb (Rheum palmatum L.), 30 g Dandelion (Taraxacum mongolicum Hand.-Mazz.) and 30 g Patrinia (Thlaspi arvense Linn.). Based upon Chinese medicine theory, Dandelion and Patrinia are the principal drugs (Monarch); Astragalus and Rhubarb are auxiliary drugs (i.e. Astragalus is the Minister, Rhubarb is the Assistant). The rationale for combining these plants is because of their heat-clearing, nourish vitality and discharging fire properties. The ratio of Astragalus, Rhubarb, Dandelion and Patrinia was 10:1:10:10. Compound Qingre Granules (QRG) were processed by Kangren Tang Pharmaceutical Company (China). QRG is prepared by following GMP standards. Patients in both QRG and Control groups, were treated as per routine practice guidelines for FUO in western medicine. Patients in the QRG group additionally received QRG two times a day for 5 days (2 bags per agents, each time one bag, 55gram/bag) as per the traditional Chinese system of medicine. Compound Qingre Granules (QRG) are composed of Astragalus, Rhubarb, Dandelion and Patrinia, and was processed by Kangren Tang Pharmaceutical Company (China). In both the groups, body temperature monitoring, inflammatory markers, length of stay in hospital and were measured.

2.4. Measurement of inflammatory markers

Peripheral blood samples were obtained in the morning. Serum was separated by centrifugation at 4500 rpm for 5 min and stored at −80 °C until further processing. The level of procalcitonin (PCT) was measured by an immunoluminometric LUMItest® PCT kit (Brahms Diagnostica Co. GmbH, Berlin, Germany). Endotoxin levels were measured by chromogenic substrate method using Limulus kits (Richmond, VA, USA). The level of C-reaction protein (CRP) was measured by immune nephelometry (Normal reference range: 0–8 mg/L).

2.5. Efficacy standards

The efficacy of heat clearing was defined as follows. 1) Fever cured: maximum body temperature within the normal range (36.0–37.2 °C), complete symptom-resolution, and no recurrence at one-month follow up; 2) Fever improved: Significant decrease in maximum temperature, but not yet within the normal range, significant symptom-resolution, or normal body temperature, but followed by recurrence of fever and symptoms at one-month follow up; 3) Fever unhealed: no significant improvement in temperature and clinical symptoms.

The efficacy rate was defined as follows:

$$\text{Efficacy rate } (\%) = [(\text{Number of cured cases} + \text{Number of improved cases})/\text{Total cases}] \times 100$$

2.6. Statistical analyses

Data from all patients were included in efficacy analyses. Continuous variables are expressed either as mean ± Standard Deviation (SD) or median ± Interquartile range (IQR). For categorical variables, the proportion in each category was calculated. One-way analysis of variance (ANOVA), Kruskal-Wallis rank-sum test, and Chi-squared test were used to assess inter-group differences.

3. Results

3.1. General information

There were 22 (17 male and 5 female) patients in the QRG group; mean age of patients was 48 years (range, 16–67) (Table 1). In the control group, there were 48 cases (29 males and 19 females); mean age was 49 years (range, 18–78 years). There was no significant difference between the two groups with respect to age, sex, duration of fever and peak temperature ($P > 0.05$).

3.2. Clinical efficacy

In the QRG group, the number of patients cured, improved and patients unhealed were 14, 7, and 1, respectively; the corresponding numbers in the control group were 25, 8 and 15, respectively

Table 1
General characteristics of study subjects by treatment group.

	QRG group	Control group	*P*
Age (years)	48.14 ± 15.75	48.52 ± 17.58	0.93
Male gender (%)	29 (60.42%)	17 (77.27%)	0.10
Duration of fever (days)	31.73 ± 29.94	57.15 ± 67.45	0.10
Peak temperature	39.29 ± 0.81	39.28 ± 0.81	0.97

QRG, Compound Qingre Granules.