

Systemic Review of RCTs focusing on Chronic Fatigue

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Objective: This study aimed to build an overview of randomized clinical controlled trials (RCTs) for chronic fatigue-related symptoms to extract the useful data for management of patients and development of therapeutics using Korean traditional medicine in the future.

Methods: All RCT-derived papers for chronic fatigue-related symptoms were collected via PubMed Database. We surveyed elementary information of RCTs such as clinical question, study design, and its quality and results.

Results: A total of fifty-three RCTs met these review criteria. Most of the RCTs were performed in Western countries, particularly the UK and USA. The major portion of RCTs focused on chronic fatigue syndrome using immune modulators, psychotherapeutic and anti-depressants. Five RCTs using complementary and alternative medicine, including herbal remedies, showed positive results.

Conclusions: Fatigue-related symptoms are a main target of Oriental medicine. This study provides helpful information for planning clinical study of chronic fatigue-related symptoms using traditional Korean medicine.

Key Words : Chronic fatigue, chronic fatigue syndrome, RCT, randomized controlled trial, traditional Korean medicine, clinical

Introduction

Fatigue is a subjective symptom, a complaint of a feeling of exhaustion or lethargy disturbing daily life. Fatigue is very prevalent among the general population, as much as 10 to 40 %¹⁻³⁾, and it is the fifth chief complaint of patients visiting family medicine clinics in South Korea^{4,5)}. Acute fatigue can generally be relieved by taking a rest or removing underlying causes. However, chronic fatigue, specifically in cases of unknown causes, is frequently problematic due to its duration and lack of effective therapies⁶⁾.

Patients with untreated chronic fatigue over six months are faced with pathogenic status regarding

physical, social, and occupational well-being⁶⁾. This chronic fatigue is considered as not peripheral fatigue but as central fatigue, and neither patho-physiologic mechanisms nor standard of treatment has yet been defined in conventional medicine⁷⁾.

Traditional Korean medicine has emphasized subjective symptoms in the process of diagnosis and treatment for diseases. Accordingly, patients in Korea with chronic fatigue-related symptoms usually visit an Oriental clinic^{8,9)}. Intensive research and therapeutic developments for chronic fatigue are increasingly required because of increasing incidence and importance to quality of life¹⁰⁾.

Recently, diverse groups have performed randomized controlled trials (RCTs) in many countries to test

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various therapeutics for chronic fatigue or chronic fatigue syndrome. This study aimed to review all RCTs related to chronic fatigue-associated symptoms, so to produce valuable information for clinical managements and studies using traditional Korean medicine in the future.

Method

1. Data source and collection

Systematic literature searches were conducted using the electronic literature PubMed Database. Studies were screened using the following inclusion criteria: (a) human subjects, (b) use of a control procedure, (c) subjects randomized among treatment conditions, and (d) examination of therapeutic efficacy of any remedies for chronic fatigue-related symptoms. The initial assessment using the inclusion criteria was made by reading abstracts. Articles that appeared to meet the criteria were then read in full.

2. Data synthesis and analysis

The data were extracted from the articles using a standardized, predefined method that considered trial objects, study design, patient characteristics, and outcomes. The RCTs were heterogeneous in aspect of therapeutics or purposes. Hence, we decided not to pool the data from specific sections statistically.

Results

1. General pattern of RCTs

Two hundred fifteen papers were initially selected under filtering conditions of both clinical trial and chronic fatigue. After reading the abstracts, fifty-three papers met the full criteria of this review study evaluating the efficacy of therapeutics for chronic fatigue or chronic fatigue syndrome using RCT.

Following the first RCT to validate the effect of acyclovir for 25 patients with chronic fatigue syndrome in 1988¹¹⁾, many RCTs have been conducted, on average 3.5 trials per year. Sixteen RCTs were performed in the UK, and more than 90% of RCTs were performed in European countries and the US (Fig 1). The five trials among Asian countries were in China, Japan and Korea, three, one and one respectively.

2. Target symptoms and treatment-related clinical question for RCT

Five of fifty-three RCTs targeted chronic fatigue including idiopathic chronic fatigue¹²⁻¹⁴⁾, whereas the rest aimed to study chronic fatigue syndrome. The most frequent treatment objects related to immune modulators such as NK cell stimulant¹⁵⁾, alpha interferon¹⁶⁾, and low dose hydrocortisone therapy¹⁷⁾. Psychotherapeutic approaches, especially cognitive behaviour therapy¹⁸⁾, anti-depressants, and nutrition

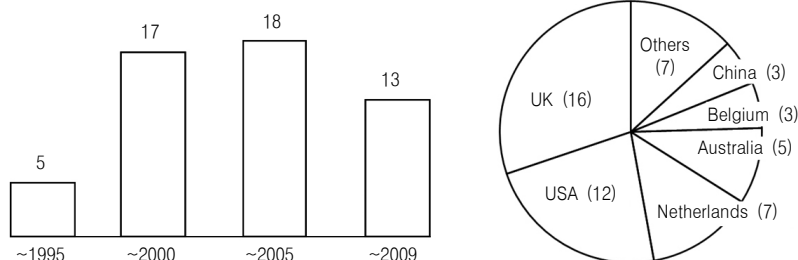


Fig. 1. Distribution of RCTs according to year (left) and country performed (right)

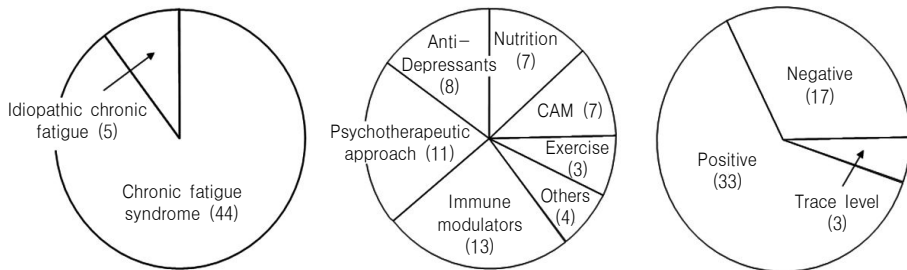


Fig. 2. Distribution of RCTs according to the specific disorders (left), main treatments (middle), or outcomes (right)

were also main objects. Seven studies were related with complementary and alternative medicine (Fig 2)¹²⁻¹⁴.

Thirty-three trials obtained positive results; the rest either showed negative outcomes or were inconclusive.

3. Analysis of RCT designs

As an aspect of RCT design, the major portion had two arms while eight RCTs had three or more arms. For the control group, twenty-eight RCTs provided a placebo but the rest compared their therapeutics with other therapies or just observation instead of placebo. The median number of participants for RCTs was 66, ranging from 12 to 434¹⁹ (Fig 3).

4. Analysis of therapeutics that showed positive outcomes

Thirty three of all RCTs showed positive results.

There were many RCTs having positive outcomes using immune modulators (gamma globulin injection¹⁹ and oral hydrocortisone treatment¹⁷). Most trials using cognitive behavior therapy or guided self-instructions showed positive results^{20,21}. Some anti-depressants such as fluoxetine, moclobemide, phenelzine, or methylphenidate showed clinical effectiveness^{22,23}. In addition, graded exercise and some nutritional measures also had positive effects^{24,25}. Especially, most complementary and alternative medicine-related RTCs using cupping, acupuncture or herbal drugs significantly reduced the severity of fatigue symptoms^{26,27}.

Discussion and Conclusion

Fatigue is a frequent complaint in primary care. In 1994, the American Centers for Disease Control and Prevention defined prolonged fatigue as over one

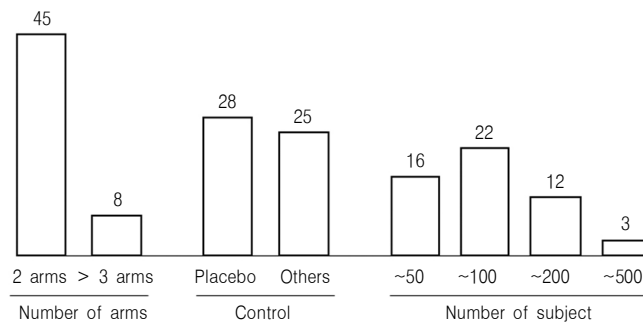


Fig. 3. Characteristics of main factors in RCT design

Table 1. Summary of anti-fatigue therapeutics with positive result in RCT

Class	Therapeutics and their characteristics
Immune modulators	Intravenous gamma globulin, Low-dose oral hydrocortisone, Poly I:poly C12U (mismatched dsRNA), High-dose IgG
Psychotherapeutic	Cognitive behavior therapy, Guided self-instructions
Anti-depressants	Fluoxetine, Moclobemide, Phenelzine, Methylphenidate
Nutrition	Acetylcarnitine, Propionylcarnitine, Amantadine
CAM	Multiple cupping, Myelophil (mix of <i>Astragali Radix</i> and <i>Salviae Radix</i>), Electrical acupuncture, Kampo formulae
Exercise	Self-managed graded exercise, Graded aerobic exercise

month up to six months of extended fatigue, and chronic fatigue for longer than six months. In particular, unexplained chronic fatigue has become a medical problem, and includes two subclass, idiopathic chronic fatigue and chronic fatigue syndrome²⁸⁾.

Epidemiological data shows that around 4.2% and 0.42% of subjects have idiopathic chronic fatigue vs. chronic fatigue syndrome respectively among 28,673 general populations in the US²⁹⁾. Of 1,648 visitors to eight Korean primary family clinics surveyed, 8.4% complained of chronic fatigue and 20% of them had no explaining medical causes. The patients who met criteria for chronic fatigue syndrome were 0.6%³⁰⁾. Despite this high morbidity of unexplained chronic fatigue, there is not yet a standard of treatment guarantying clinical improvement⁷⁾. So, many groups have studied its pathogenesis and therapeutics, and various RCTs to evaluate efficacy have been performed.

It was found that 94% of RCTs targeted chronic fatigue syndrome rather than idiopathic chronic fatigue, and most RCTs for chronic fatigue were conducted in western countries. The reason is anticipated that chronic fatigue has been more frequently problematic in developed western countries than in Oriental countries. Chronic fatigue syndrome is characterized by strictly defined criteria. It is known to have profound fatigue, neuropsychiatric dysfunction, and frequent abnormalities in cell-mediated immunity³¹⁾. Accordingly, various immune-related therapeutics were evaluated using RCTs, particularly in the earlier

period of study. The findings were controversial; since then, the main objects of RCT seemed to have shifted to psychotherapeutics or exercise.

Currently, no curing therapeutics for patients with chronic fatigue syndrome or idiopathic chronic fatigue have yet been developed. These disorders are recognized to be connected to psychological disturbances such as depression. Anti-depressants partially improved the clinical symptoms of chronic fatigue in some RCTs, but other trials showed no effect. A systematic review found cognitive-behavioural therapy and graded exercise to be promising treatments for chronic fatigue syndrome³¹⁾. Seven RCTs with cognitive behavior therapy were done, and their results were all positive except one³¹⁾.

Chronic fatigue greatly affects quality of life and conventional therapy is often of limited help. This status leads fatigued patients to seek complementary and alternative medicine, including herbal treatments. There were RCTs using multiple cupping²⁶⁾, a herbal mixture of *Astragali Radix* and *Salviae Radix*¹²⁾, electrical acupuncture²⁷⁾, and *kampo* formulae¹³⁾, which had significant effects on chronic fatigue. These results indicate that traditional Korean medicine has a high potency to be a main therapeutic for chronic fatigue-related symptoms. We need more systematic and scientific researches on remedy development for chronic fatigue. Traditional Korean medicine has developed many therapeutics associated with chronic fatigue, such as herbal formulae. At present, clinical-

based research such as RCT is strongly required.

Fatigue-related symptoms will remain prevalent and be a potential target of traditional Korean medicine in the future. In conclusion, the author hopes that this study could provide helpful information in process of valuable therapeutics using traditional Korean medicine.

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