

Effects of moderate whole-body hyperthermia and complementary medicine in the treatment of rheumatoid arthritis: a preliminary study

Siddarth Agrawal

Integrative Medical Center Sp. z o. o.
Poland

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Abstract

It is estimated that more than two-thirds of patients with rheumatoid arthritis (RA) use complementary and alternative medicine (CAM). The rationale for the use of some CAM therapies is supported by reasonable evidence. 8 patients with RA were included in the preliminary study. Patients received treatment that included whole-body hyperthermia, ozone major autohemotherapy, intravenous vitamin C and individual nutrition counselling for 4 weeks. The patient's perceptions of pain, stiffness, and fatigue were measured on a 100-mm visual analogue scale and were considered as primary outcomes. In all patients, a significant improvement was seen at the end of the treatment and post-treatment. Pain and stiffness reduced over 40%, while fatigue nearly 60% for patients with RA. More importantly, the treatment was found to be safe and did not relate with any adverse events. The results of this study are encouraging and may become a platform for future planning of long-term studies with the complementary treatments in combination with existing standard therapies in RA.

Introduction

Rheumatoid arthritis (RA) is a symmetric, inflammatory, peripheral polyarthritis of unknown aetiology, which affects multiple small joints of the hands and feet. The evolution of hyperplastic synovial tissue, leads to deformity through the stretching of tendons and ligaments and destruction of joints through the erosion of cartilage and bone.

It is estimated that 60% to 90% of persons with arthritis, particularly those with rheumatoid arthritis, have used complementary and alternative medicine (CAM) [1]. The rationale for the use of some therapies is supported by a reasonable and fairly consistent body of evidence.

Heat treatment in patients with rheumatic disorders has been used through the ages. Initially, the application of hyperthermia treatment was mainly empirical. In the last few decades evidence from clinical studies documented its beneficial effects in RA [2,3]. Pain and stiffness decrease, and grip strength and range of motion improve after application of local hyperthermia [4]. Some studies reported beneficial effects of whole-body hyperthermia (WBH) [5,6].

In this preliminary study, the effectiveness of whole-body hyperthermia and complementary therapies in the treatment of rheumatoid arthritis was evaluated.

Material and methods

8 patients with RA were included in the study. Patients received treatment for 4 weeks. After oral and written information about the treatment and the possible clinical effects of applied therapies, patients were invited to the study. Informed consent was obtained from all patients. Clinical measurements were performed before the start of the treatment, at the end of the 4-week period of therapy and one month after the end of the treatment series. The patient's perceptions of pain [7], stiffness [8], and fatigue [9–11] were measured on a 100-mm visual analogue scale and were considered as primary outcomes.

Statistical analysis

The conformity assessment was carried out by the Shapiro-Wilk test. The homogeneity of variance was tested with Bartlett's test. The significance of differences in mean values (M) in more than two populations for parameters of normal distribution and of homogeneous variances was assessed with analysis of variance (ANOVA). In case of rejection of the null hypothesis of homogeneity of variance, to verify the differences between the mean values in pairs, post-hoc tests were performed (Scheffe test). The level $p = 0.05$ was assumed as the critical significance level. Data was expressed as $M \pm SD$ and analysed with the statistical program STATISTICA v.12 (StatSoft, Inc. Tulsa, USA).

Treatment protocol

The treatment protocol consisted of: 4 moderate whole-body hyperthermia sessions (once every week), 8 sessions (twice every week) of ozone major autohemotherapy (MAHT) and intravenous vitamin C (IVC), as well as two individual nutrition counselling.

Results

Patient characteristics. A total of 8 patients (6 female, 2 male) with RA were included in the study with mean age of 51 (Table 1). One patient dropped out in the treatment period due to nonmedical reasons and could not be measured for follow-up. Hence, the mean group results of 7 patients are presented in Table 2. Pain and stiffness ($p < 0.05$) as well as fatigue ($p < 0.001$) significantly decreased at the end of the treatment and post-treatment periods.

Discussion

In all patients, a clinically significant improvement was seen at the end of the treatment and post-treatment. Pain and stiffness reduced over 40%, while fatigue nearly 60% for patients with RA (Table 2). The effect of whole-body hyperthermia upon local joint inflammation or disease activity is not clear. The findings of earlier studies were ambiguous [12-18], and many studies have no optimal quality as summarized in the COCHRANE study [2]. It is known that whole-body hyperthermia can enhance immune surveillance, including increased mobility and activity of white blood cells [19,20]. It is hypothesized that increased temperature can modulate the immune response by targeting the intracellular signalling pathways, cytokines, and other mediators of the phases of RA.

Ozone major autohemotherapy was first described in 1954 [21] and since then, after Wolff's modification [22], it has been carried out worldwide millions of times without side-effects and with therapeutic results [23]. The rationale for the use of ozone is based on its immunosuppressive action if it is used at high concentration (45-65 $\mu\text{g}/\text{ml}$) [24]. Several studies described its anti-inflammatory and analgesic effects [25,26], the functional recovery of muscle and joint groups [27,28], as well as perfusion improvement of

microcirculation [29]. A study by Chang et al. demonstrated that ozone applied externally ameliorated the inflammatory reaction of RA without toxicity or serious side effects [30]. The authors found that the decrease in cytokine synthesis and secretion was due to the pouring of ozone into the inflamed and infiltrated area via oxidation and eliminating the hyperplastic synovial fibroblasts. Our study showed that ozone in the form of MAHT was well-tolerated and contributed to the beneficial outcome of the therapy.

Oxidative stress and severe systemic inflammation have been considered as important pathophysiologic mechanisms involved in the development of RA [31, 32]. Oxidative stress occurs in response to the oxidative damage resulting from imbalance between antioxidant and scavenging ability and the active oxidants produced by a harmful stimulant [32, 33]. Previous reports showed that significantly elevated production of reactive oxygen species (ROS) in the serum of RA patients can be observed comparing with healthy donors [34]. ROS are indirectly involved in joint damage as the secondary messengers in inflammatory and immunological cellular response in RA, which also can degrade directly the joint cartilage, influencing its proteoglycan and inhibiting its synthesis [35, 36].

In this study, the rationale for the use of IVC and diet modification has been based on their anti-inflammatory action. Vitamin C has direct antioxidant capacity and contributes to the protection of cells from the damaging effects of endogenously produced or exogenous reactive oxygen radicals and reactive nitrogen species, e.g. during immune activation. Vitamin C prevents oxidative damage to lipids, proteins, and DNA, which has been implicated as a major contributing factor in the development of chronic diseases such as cardiovascular disease, cancer, and cataract, respectively [37,38]. Evidence further suggests that vitamin C provides indirect antioxidant protection by regenerating other biologically important antioxidants such as glutathione and vitamin E to their active state [39]. The nutritional and physiological aspects of this essential nutrient have been widely reviewed in a large number of comprehensive publications on vitamin C [37,40]. To our knowledge, this is the first study that evaluated the demonstrated that IVC is safe and does not correlate with any adverse events.

Among a number of small clinical trials of dietary manipulation in RA, modest benefit has been noted for high-dose omega-3 fatty acids, fasting, vegetarian diet, and Mediterranean-type diet [41-43]. In a recent study by Tedeschi et al. [44] 24.0% of subjects in a prospective,

longitudinal RA registry reported that foods affect their RA symptoms, and 24.3% avoid foods due to worsening of their RA. Among a list of 20 specific foods, blueberries and spinach were most often noted to improve RA, while soda with sugar and desserts were most commonly reported to worsen RA. Past work has shown that greater consumption of sugar-sweetened beverages is associated with increased risk for developing RA [45].

In this study, a certified nutritionist provided face-to-face counselling that was individually tailored to each patient. Each counselling session lasted 30 to 60 minutes, during which nutritionists educated and strongly recommended patients to follow an anti-inflammatory diet. The Western-type diet, which is high in red meat, high-fat dairy products, refined grains, and simple carbohydrates, has been associated with higher levels of CRP and IL-6 [46]. On the other hand, the anti-inflammatory Mediterranean diet, which is high in whole grains, fish, fruit and green vegetables, and associated with moderate alcohol and olive oil intake and low intake of red meat and butter has been associated with lower levels of inflammation [47–51]. Diets high in fruit and vegetable intake have been associated with lower levels of CRP [52–54]. Specific nutrients such as (n-3) fatty acids [55–56], fiber [57–58], moderate alcohol intake [59–60], vitamin C [61–62], β -carotene [63–64], and magnesium [65–66] have also consistently been shown to be associated with lower levels of inflammation. In our study, we observed that individual counselling can greatly affect engagement and compliance to the prescribed diet. Post-treatment all patients reported that they follow the dietary guidelines.

In conclusion, WBH and complementary therapies were safe and well-tolerated when given up to 4 weeks. Although our present data are limited in terms of small sample size and lack of control group they are encouraging and may become a platform for future planning of long-term studies with the complementary treatments in combination with existing standard therapies in RA. The multifaceted approach presented in this research consisted of immunomodulating heat therapy in the form of WBH, immunosuppressive and regenerative therapy in the form of MAHT and anti-inflammatory IVC and nutritional counselling. While we cannot draw strong conclusions based on this study, the suggested multimodal approach may be beneficial in the management of refractory RA.

Tables

Table 1

Gender	2 males, 6 females
Age	51 yrs. [SD=11.21; range=33-63]
Disease duration	8.2 yrs. [SD=6.36; range=1-17]

Table 2

	Before treatment	End of treatment	Post-treatment
Pain	44 (4)	24 (5)*	25 (5)*
Stiffness	38 (6)	21 (3)*	23 (4)*
Fatigue	41 (7)	17 (3)**	18 (4)**

VAS, 0–100 mm; mean (SD), *p<0.05; ** p<0.01 vs. before treatment

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