Effectiveness of different cryotherapies on pain and disease activity in active rheumatoid arthritis. A randomised single blinded controlled trial

H.E. Hirvonen1, M.K. Mikkelsson1, H. Kautiainen1, T.H. Pohjolainen2, M. Leirisalo-Repo3

1Rheumatism Foundation Hospital, Heinola, Finland; 2Orton, the Rehabilitation Unit of the Invalid Foundation, Helsinki; 3Helsinki University Central Hospital, Helsinki, Finland.

Abstract

Objective

Local cryotherapy is used to relieve pain and inflammation in injuries and inflammatory conditions. Whole-body cryotherapy is an extreme method administered at -110 ºC for 2 to 3 minutes. The aim of the study was to compare the effect of cryotherapies on pain and inflammation in patients with rheumatoid arthritis (RA).

Methods

Sixty patients with active seropositive RA were recruited in a randomised controlled single-blinded study to receive whole-body cryotherapy at -110 ºC, whole-body cryotherapy at -60 ºC, application of local cold air at -30 ºC and the use of cold packs locally. In the final analysis, the last 2 groups were pooled. The patients had 2-3 cryotherapy sessions daily for one week plus conventional physiotherapy. Clinical and laboratory variables and patient’s and physician’s global assessments were used to assess the outcome. Disease activity was calculated by DAS.

Results

Pain decreased in all treatment groups, most markedly in the whole-body cryotherapy (-110 ºC) group. DAS decreased slightly with no statistically significant differences between the groups. No serious or permanent adverse effects were detected. Six of 40 patients (15%) discontinued the whole-body cryotherapy.

Conclusion

Pain seemed to decrease more in patients in the whole-body cryotherapy at -110 ºC than during other cryotherapies, but there were no significant differences in the disease activity between the groups. However, cryotherapy at -110 ºC is expensive and available only in special centres and may have minor adverse effects. Based on our results, whole-body cryotherapy at -110 ºC is not superior to local cryotherapy commonly used in RA patients for pain relief and as an adjunct to physiotherapy.

Key words

Rheumatoid arthritis, pain, cryotherapy, rehabilitation.

Clinical and Experimental Rheumatology 2006; 24: 295-301.
Cryotherapies in active rheumatoid arthritis / H.E. Hirvonen et al.

Hanna E Hirvonen, MD; Marja K Mikkelsson, MD, Associate Professor; Hannu Kautiainen, BA, biostatistician; Timo H Pohjolainen, MD, PhD, Associate Professor; Marjatta Leirisalo-Repo, MD, PhD, Professor.

This study was supported by the Social Insurance Institution and the Ministry of Social Affairs and Health, Finland, PATU Development Project of the Rheumatism Foundation Hospital, and the European Social Fund of the European Commission and the Provincial State Office of Southern Finland.

Please address correspondence and reprint requests to: Hanna Hirvonen, MD, Reumasäätiön sairaala, Pikijärventie 1, FI-18120 Heinola, Finland. E-mail: hanna.hirvonen@pp4.inet.fi

Received on October 24, 2005; accepted in revised form on February 24, 2006. © Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2006.

Introduction
Rheumatoid arthritis (RA) is a chronic inflammatory and destructive joint disease. Decreased mobility due to chronic pain and morning stiffness suppress the quality of life of the patients and cause functional disability. Previous studies have shown that physical activity is beneficial in RA, even in patients with active disease (1-3). An effective non-pharmacological method to relieve pain and inflammation would decrease the need for non-steroidal anti-inflammatory drugs (NSAID) which often cause adverse gastrointestinal effects, and would also improve the patients’ ability to exercise.

In an arthritic joint the temperature increases (4, 5). Local cryotherapy e.g. with cold packs is widely used to alleviate pain in inflammatory diseases, injuries and overuse symptoms. In in vitro studies the increase of local temperature accelerated cartilage collagenolysis (6). A temporary decrease in intra-articular temperature, lasting at least for three hours, is achievable with local cold therapy (5, 7, 8), and with intra-articular glucocorticoid injections (9). Based on these findings, local cryotherapy has been recommended for patients with active arthritis. In the north, winter swimming in cold water is a traditional modification of cold therapy approved by a proportion of rheumatic patients to relieve pain and inflammation and to increase a feeling of general well-being.

Whole-body cryotherapy in a room with a temperature of -110°C is an extreme form of cryotherapy, introduced and modelled for therapeutic purposes by Yamauchi in 1970s (10). In Europe the treatment was adopted in Germany in 1984-1985 (11). The trials of whole-body cryotherapy have included small numbers of patients, demographic data of patients has been limited and the studies have not been properly randomised. Most studies have been published only as abstracts or congress reports and details of the experiments are not available.

Studies on physiological effects of cold air and cold water and whole-body cryotherapy on healthy young subjects have shown that skin temperature decreases abruptly, but a moderate cold impulse of short duration does not have any significant effect on core temperature (12-16). Taghawinejad and coworkers noticed a mean change of -0.38°C in sublingual temperature in 229 persons during -100°C whole-body cryotherapy in 90 seconds (17). Simultaneously the metabolic rate increases and a rise in blood pressure can be detected (13-15, 18). There are inter-individual differences in the capacity to resist cold (19). A painless period up to two hours has been observed following one visit to the whole-body cryotherapy room at -110°C (20-22). Decreased duration of morning stiffness, a feeling of better general health, a decrease in disease activity and an increased pain threshold have been reported in rheumatic patients (22-25). The therapeutic target is not hypothermia. It is believed that whole-body cryotherapy acts via neuroendocrinological, humoral and immunomodulative mechanisms and induces body hardening (26-29).

Although evidence of its effectiveness was limited, whole-body cryotherapy was started in Finland at the Rheumatism Foundation Hospital in August 2000. As little is known about the effects of various cryotherapies on pain and disease activity in patients with RA, we carried out a study to compare the effects of whole-body cryotherapy (-110°C) with whole-body cryotherapy (-60°C) and local cryotherapy as an adjunct to physiotherapy in patients with active RA.

Patients and methods
Study population
The study was carried out during the period from September 2000 to May 2003. RA patients from all over Finland who were referred by the treating physician and accepted by the Social Insurance Institution for a treatment period for 8 days - 3 weeks at the Rheumatism Foundation Hospital because of active or seriously disabling arthritis were informed about the study beforehand and asked to participate. The patients were examined at entry to the hospital. Patients who had active seropositive RA were eligible for the study if they fulfilled the following...
inclusion criteria: 5 or more swollen and 5 or more tender joints, erythrocyte sedimentation rate (ESR) 20 mm/h or greater at inclusion and/or C-reactive protein (CRP) concentration in serum greater than 20 mg/l, and a duration of morning stiffness of 30 minutes or more. The medication had to be stable for at least one month before the study and no intra-articular glucocorticoid injections carried out during the previous month. The exclusion criteria included uncontrolled hypertension (diastolic blood pressure over 100 mmHg), a history of cardiac arrhythmia, symptomatic cardiovascular or lung disease, severe Raynaud’s phenomenon, cold allergy or cold induced bronchospasm. During the study period there were 1098 possible patients with seropositive RA for the cryotherapy trial. Of these, 928 were not eligible, 796 because they did not meet the inclusion criteria, 170 were eligible for the study, but 110 refused. (Fig. 1) Thus, the final number of patients included is 60.

Study design
At the beginning, the target was 160 patients, randomised in 4 groups (local cold packs, local cold air -30°C, whole-body cryotherapy at -60°C or whole-body cryotherapy at -110°C). However, the recruitment rate was very slow due to the strict inclusion criteria. At the time when the study had been ongoing for two and a half years, we lowered the target to 60 patients, and combined the two local cold groups. Thus, 60 patients who fulfilled the criteria were included in the study, 20 in each group. On arrival the patients were randomised to use traditional local cryotherapy (cold packs or cold air -30°C), whole-body cryotherapy at -60°C or whole-body cryotherapy at -110°C. To maintain and improve the range of motion of joints, the patient also had individual physiotherapy or low impact group exercise for arthritis not more than twice a day. The medication was stable and no glucocorticoid injections were given during the trial.

A rheumatologist (HEH) blinded for the treatment arm examined the patients on day 0 before any therapies and on day 7 after the last cryotherapy. She recorded the number of swollen and tender joints and the duration of morning stiffness. Blood samples were taken before the first cryotherapy and after the last cryotherapy for evaluation of sensitive CRP by an immunoturbidimetric method (Orion Diagnostica Cat.No.68025 Espoo, Finland) with the lowest sensitivity level of 0.3 mg/l. In addition, ESR by Westergren was examined.

At baseline and at the end of the study pain was measured by visual analogue scale (VAS, 0-100mm) and general well being (VAS, 0-100mm) assessed by both the patients and the blinded rheumatologist (global assessment). In addition, disease activity was expressed by DAS (30). A blinded physiotherapist measured hand grip strength of the patient on days 0, 2, 4, 6 and at the end of the study at the same time of the day. Hand grip strength was measured in kilograms (kg) using a hand dynamometer (Digitest Force, Finland). The subject was seated with his/her elbow angle adjusted at 90°. The grip of the dynamometer was adjusted to the size of the hand. The subject performed three tries with both hands, and the mean value of the best results of each hand was calculated. Radiographs of hands and feet were obtained if the latest radiographs were older than 6 months. The x-rays were read by an experienced radiologist and

Fig. 1. Trial profile.
Cryotherapies in active rheumatoid arthritis / H.E. Hirvonen et al.

scored by the Larsen method (31), by the modification of Kaarela and Kautiainen (32).

All the patients gave their written informed consent. The study protocol was approved by the ethical committee of Päijät-Häme Hospital district.

Statistical analysis
The outcome was analyzed using the last observation carried forward (LOCF) principle. The results were expressed as means, standard deviations (SD) and 95 per cent confidence intervals (CI), medians and interquartile ranges (IQR). The statistical significance was evaluated by analysis of covariance (ANCOVA) with the baseline value as covariable or Kruskal-Wallis test and chi-square test. Post hoc testing of several univariate comparisons were made with Sidak's test. The normality of variables was evaluated by the Shapiro-Wilk test. The $\alpha$ level was set at 0.05 for all tests.

Results
Clinical and radiographic characteristics of patients at baseline are shown in Table I. There were differences between the groups in age ($p = 0.004$) and disease activity measured by the original DAS ($p = 0.016$), BMI ($p = 0.044$), HAQ ($p = 0.047$) and physician’s global assessment of general well being ($p = 0.040$). The local cryotherapy group had the highest mean age, disease activity and HAQ whereas BMI was highest in the whole-body cryotherapy (-110°C) group. Medication of the patients is shown in Table II. Regular and occasional use of NSAIDs have not been differentiated. The patients were asked to take NSAIDs and other pain killing drugs in the same way as they were used to.

All 20 patients in the local cryotherapy group completed the study. Three (15%) discontinued the whole-body cryotherapy (-60°C) and three (15%) the whole-body cryotherapy (-110°C), all in the early phases of the intervention. Of the planned cryotherapy sessions 98% were carried out in the local cryotherapy group and 83% and 80% in the whole-body cryotherapy -60°C and -110°C groups respectively, including the drop out patients. The main clinical results are presented in Table III. During all modalities of cryotherapy, the DAS showed a slight but statistically significant reduction in all groups without significant difference between the groups. Pain decreased significantly in the local and whole-body cryotherapy (-110°C) groups during the seven day intervention period. The decrease was statistically significantly greater in the group of whole-body cryotherapy at -110°C than in the whole-body cryotherapy at -60°C or in the local cryotherapy group. No statistically significant changes were observed in the ESR or CRP levels. Physician’s global assessment improved in all groups.

Local cryotherapy was well tolerated. Of the 20 patients, 19 felt local cryotherapy acceptable or at least tolerable and one patient did not answer this question. Four cases of minor adverse effects were recorded in this group; two cases of respiratory infection and one patient found that joint pain became worse.

Table I. Baseline demographic, clinical and radiographic characteristics of patients.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Local cold (N = 20)</th>
<th>Cryotherapy -60°C (N = 20)</th>
<th>Cryotherapy -110°C (N = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (Female/Male)</td>
<td>16/4</td>
<td>18/2</td>
<td>17/3</td>
</tr>
<tr>
<td>Age (years), mean (range)</td>
<td>58 (50 – 73)</td>
<td>52 (37 – 65)</td>
<td>50 (21 – 64)</td>
</tr>
<tr>
<td>Duration of disease (years), median (range)</td>
<td>16 (11 – 35)</td>
<td>17 (11 – 44)</td>
<td>12 (11 – 32 )</td>
</tr>
<tr>
<td>Body Mass Index (Kg/m²), mean (SD)</td>
<td>25.7 (4)</td>
<td>24.6 (3.6)</td>
<td>28.3 (5.9)</td>
</tr>
<tr>
<td>Clinical:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of morning stiffness (min), median (IQR)</td>
<td>120 (60 , 240)</td>
<td>60 (60 , 120)</td>
<td>90 (45 , 150)</td>
</tr>
<tr>
<td>Health Assessment Questionnaire (HAQ), median (IQR)</td>
<td>1.62 (0.87 , 2.22)</td>
<td>1.00 (0.75 , 1.11)</td>
<td>1.12 (0.75 , 1.72)</td>
</tr>
<tr>
<td>Radiographic:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of x-ray pictures available</td>
<td>20</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>Larsen score (0-100), median (IQR)</td>
<td>40 (12 , 90)</td>
<td>38 (10 , 75)</td>
<td>23 (4 , 67)</td>
</tr>
</tbody>
</table>

Table II. Numbers of patients on DMARDs and other medications at baseline.

<table>
<thead>
<tr>
<th></th>
<th>Local cold (N = 20)</th>
<th>Cryotherapy -60°C (N = 20)</th>
<th>Cryotherapy -110°C (N = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMARD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytostatics</td>
<td>10</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>10</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Median dose, mg (range)</td>
<td>5.0 (5.0-100)</td>
<td>5.0 (2.5 – 15.0)</td>
<td>5.0 (2.5 - 7.5 )</td>
</tr>
<tr>
<td>NSAID</td>
<td>16</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Thyroid hormone</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

NSAID: non-steroidal anti-inflammatory drugs (includes both regular and occasional use).
DMARD: disease modifying anti-rheumatic drugs (excluding cytostatics).
Cryotherapies in active rheumatoid arthritis / H.E. Hirvonen et al.

Discussion

This is the first randomised controlled trial of whole-body cryotherapy for patients with RA. The results showed that during the seven day treatment period of patients with active RA, both the patient’s and the physician’s global assessments showed an amelioration during the treatment period. In addition, there was a decrease of pain in patients in both the local cryotherapy and whole-body cryotherapy at -110°C groups but there was no change in the activity of the disease. Of the several variables, change in the patients’ report of pain was the only one in favour of whole-body cryotherapy at -110°C. Unfortunately, our randomised study groups were not identical. There were differences both in demographic and clinical data. The study sample was smaller than expected at the time we planned the study. It was not easy to find voluntary patients who fulfilled the strict activity and stability inclusion criteria even at the Rheumatism Foundation Hospital, which traditionally focuses on rehabilitation of rheumatic patients with severe rheumatic disease.

The main reasons for refusal were that the patient felt uncomfortable with the idea of cryotherapy, she/he could not stay in hospital long enough for personal reasons, or the patient required local glucocorticoid injections at entry. In most studies cryotherapy has been combined with physical exercise as in the present study. The content of the reference therapies has varied greatly. Several studies have used local heat therapy as a control therapy (21, 24) or traditional physical exercise without cryotherapy (23). Richter et al mention in an abstract that they had whole-body cryotherapy -60°C as control therapy (29). We did not have a control group

<table>
<thead>
<tr>
<th>Variables</th>
<th>Local cold (N = 20)</th>
<th>Cryotherapy -60°C (N = 20)</th>
<th>Cryotherapy -110°C (N = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory infection</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Fiebre</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Urticaria</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Long lasting freezing</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Malaise</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Joint or muscle pain</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Nervousness</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

15 patients with 17 adverse effects.
Cryotherapies in active rheumatoid arthritis / H.E. Hirvonen et al.

with only physiotherapy twice a day, an evident weakness of this study. Instead we used physiotherapy in all patients with the goal of maintaining the range of movement of joints; other physical pain treatment methods were not allowed. Therefore, it is unlikely that physiotherapy would have caused bias in the study.

The result of pain relief is in accordance with previous studies (20, 25). Pain intensity reduced clearly during the whole period of seven days. Global assessment of general well being improved, as in a previous report of whole-body cryotherapy (22), but differences between the local and whole-body cryotherapy groups were not found. Byrne and coworkers have reported better joint function after whole-body cryotherapy (22), but we did not use any tests to measure joint mobility. Laboratory variables measuring inflammation (ESR or CRP) did not change significantly, as also reported by Byrne and coworkers (33).

Adverse effects were frequently reported; five patients (25%) mentioned that whole-body cryotherapy at -110°C caused side effects, most of which were mild. The main adverse effect was a feeling of discomfort and two patients discontinued the trial because of it. The profile of side effects fits well with our clinical experience and previous reports of whole-body cryotherapy (17, 20). Using pre-screening and excluding patients with uncontrolled hypertension, cardiac or lung problems, cold allergy or circulatory problems, we have used whole-body cryotherapy at our institution for about five years and as an adjunct to physiotherapy.

Acknowledgements

We thank Dr. Irma Soim, PhD, for reading the radiographs, Tarja Westerlund, MSc, physiotherapist, for measuring grip strengths, and Riitta Lahiri for assisting the study.

References

Cryotherapies in active rheumatoid arthritis / H.E. Hirvonen et al.