

## Cryotherapy decreases histamine levels in the blood of patients with rheumatoid arthritis

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### Abstract

**Introduction** Conventional physiotherapy (electrotherapy, magnetic fields), kinesitherapy, and whole-body cryotherapy (plus kinesitherapy) are used to relieve pain and inflammation or to improve function in rheumatic diseases. The aim of this study was to investigate the effects of different physiotherapies and cryotherapy on biochemical blood parameters of patients with rheumatoid arthritis (RA) and osteoarthritis (OA).

**Materials and methods** Twenty patients with RA and 17 patients with OA received whole-body cryotherapy at  $-140$  to  $-160^{\circ}\text{C}$  for 2 to 3 min, once daily for 4 weeks. The second group of patients (24 with RA and 28 with OA) received conventional physiotherapy for 4 weeks. We measured the parameters of neutrophil activation (respiratory burst, calprotectin) and markers of cartilage metabolism [*N*-acetyl-beta-*D*-hexosaminidase (NAHase), ectonucleotide pyrophosphohydrolase (NTPPHase)] twice: before and 3 months after cryotherapy or physiotherapy.

**Results** We showed, for the first time, that cryotherapy significantly reduced ( $P < 0.001$ ) histamine levels in the blood of patients with RA. The effect was long-lasting (for at least 3 months). The levels of blood histamine in patients with OA were not changed significantly. Cryotherapy also downregulated the respiratory burst of PMNs and NAHase activity and upregulated calprotectin levels and the activity of NTPPHase. However, these changes were not statistically significant. In contrast, there were no significant changes in histamine levels or the other biochemical parameters measured in groups of patients treated only with physiotherapy and kinesitherapy.

**Conclusion** It may be concluded that the beneficial clinical effects of cryotherapy in RA patients are in part due to the action on the production, release, or degradation of histamine.

**Keywords** Rehabilitation · Cryotherapy · Histamine · Respiratory burst · Cartilage metabolism

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### Introduction

Conventional physiotherapy (electrotherapy, magnetic fields), kinesitherapy, and whole-body cryotherapy (plus kinesitherapy) are used to relieve pain and inflammation or to improve function in rheumatic diseases. Cryotherapy is a method of applying an air flow, cooled with the vapor of liquid nitrogen to a temperature lower than  $-100^{\circ}\text{C}$ , either locally to the selected joint or to the whole body in a cryosauna.

The aim of this study was to investigate the effects of different physiotherapies and cryotherapy on biochemical blood parameters of patients with rheumatoid arthritis (RA) and osteoarthritis (OA).

**Table 1** Effect of rehabilitation on biochemical blood parameters of patients with RA

	Cryotherapy		Physio- and kinesitherapy	
	Before	After	Before	After
Histamine (ng/ml)	122.8 ± 52.5	46.1* ± 28.7	113.0 ± 25.8	88.5 ± 43.7
Chemiluminescence (mV × 30 min/10 <sup>5</sup> cells)	1,188.9 ± 1207.1	901.1 ± 839.3	861.0 ± 675.3	567.0 ± 390.6
Calprotectin (units)	261.0 ± 151.4	301.1 ± 160.1	223.2 ± 141.2	258.0 ± 170.6
NAHase (units)	25.6 ± 7.3	21.6 ± 6.7	23.8 ± 7.4	21.1 ± 4.6
NTPPHase (units)	1,639.1 ± 643.5	1,803.2 ± 488.3	1,498.7 ± 223.7	1,865.7 ± 440.1

\* $p < 0.001$  as compared with group of patients before cryotherapy

Biochemical parameters in blood were measured twice: before and 3 months after cryotherapy or physiotherapy

**Table 2** Effect of rehabilitation on biochemical blood parameters of patients with OA

	Cryotherapy		Physio- and kinesitherapy	
	Before	After	Before	After
Histamine (ng/ml)	99.1 ± 47.0	79.1 ± 51.9	133.1 ± 47.3	103.1 ± 47.1
Chemiluminescence (mV × 30 min/10 <sup>5</sup> cells)	786.0 ± 505.3	728.1 ± 637.8	746.0 ± 608.8	726.0 ± 319.3
Calprotectin (units)	189.9 ± 112.1	208.6 ± 88.8	151.6 ± 101.5	205.6 ± 103.3
NAHase (units)	26.4 ± 8.2	24.9 ± 7.7	25.3 ± 3.1	24.5 ± 3.7
NTPPHase (units)	1,581.3 ± 286.1	1,670.5 ± 376.1	1,629.7 ± 521.5	1,786.2 ± 291.2

Biochemical parameters in blood were measured twice: before and 3 months after cryotherapy or physiotherapy

## Materials and methods

Forty-four patients with RA and 45 patients with OA, according to the American College of Rheumatology (ACR) diagnostic criteria [1, 2], were enrolled in this study. The pharmacological treatment of all of the patients remained unchanged for the whole period of the study and for 3 months beforehand. Twenty patients with RA and seventeen patients with OA received whole-body cryotherapy at  $-140$  to  $-160^{\circ}\text{C}$  for 2–3 min, once daily for 4 weeks. The second group of patients received conventional physiotherapy for 4 weeks. Blood levels of histamine, chemiluminescence of PMNs, and serum levels of calprotectin, *N*-acetyl-beta-*D*-hexosaminidase (NAHase) and ectonucleotide pyrophosphohydrolase (NTPPHase) were measured twice: before and 3 months after cryotherapy or physiotherapy.

Histamine in whole blood was determined fluorimetrically after chromatography on Dowex 5W × 8 and two stage extraction (n-butanol, heptane), using the *o* phthaldialdehyde method of Shore et al. [4]. The chemiluminescence assay was performed at  $37^{\circ}\text{C}$  in final volume of 1 ml PBS supplemented with 0.1% bovine serum albumin and 0.1% glucose containing  $10^5$  neutrophils, luminol (150 mM) plus

opsonized zymosan (1 mg) and measured as the total light generation after 30 min using a BioOrbit 1251 Luminometer as described previously [5]. NAHase and NTPPHase activity in serum was measured colorimetrically (units of p-nitrophenol per hour per milliliter). Calprotectin was determined using a commercial ELISA test kit.

Data are expressed as means ± SD. One-way ANOVA followed by Tukey's test was applied to evaluate the effect of rehabilitation.  $P < 0.05$  was considered to be statistically significant.

The study was approved by the local Ethics Commission, and the experiments were performed according to the national ethics guidelines.

## Results and discussion

Rheumatoid arthritis is a chronic auto-inflammatory disease characterized by synovial inflammation and progressive bone destruction that leads to joint deformity and physical disability [3]. OA is also a chronic disease characterized by irreversible damage to joint structure, including loss of articular cartilage, osteophyte formation, alteration in subchondral bone, and synovial inflammation

[2]. Pain, functional disability, and impairment of health-related quality of life are major complaints in patients with both diseases. Pharmacotherapy, together with rehabilitation, leads to a reduction in disease-related activity parameters in patients suffering from RA and OA. We here determined the effect of rehabilitation on histamine levels in blood, the parameters of neutrophil activation (respiratory burst, calprotectin), and markers of cartilage metabolism (NAHase, NTPPHase).

The data are presented in Tables 1 and 2. We showed, for the first time, that cryotherapy significantly ( $p < 0.001$ ) reduced histamine levels in the blood of patients with RA. The effect was long-lasting (for at least 3 months). The levels of blood histamine in patients with OA were not changed significantly. Cryotherapy also down-regulated the respiratory burst of PMNs and NAHase activity and up-regulated calprotectin levels and the activity of NTPPHase. However, these changes were not statistically significant. In contrast, there were no significant changes in histamine levels or the other biochemical parameters measured in groups of patients treated only with physiotherapy and kinesiotherapy.

It may be concluded that the beneficial clinical effects of cryotherapy in RA patients are in part due to the action on the production, release, or degradation of histamine.

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