Whole-body cryotherapy for the treatment of rheumatoid arthritis: a monocentric, single-blinded, randomised controlled trial

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Abstract

Objective

To evaluate effects of whole-body cryotherapy (WBC) in rheumatoid arthritis (RA).

Methods

Patients with active RA undergoing a 16-day multimodal rheumatologic complex treatment were randomly assigned to either WBC (6 applications in 14 days at -130°C for 3 min) or no treatment. The primary outcome was the difference between groups in pain on a numerical rating scale after intervention. Secondary outcomes assessed effects on i) disease activity, ii) functional capacity, iii) cytokine levels, and iv) use of analgesics.

Results

A total of 56 RA patients completed the trial (intervention group [IG]: 31 patients, control group [CG]: 25 patients). The mean change (± standard error) in pain after intervention was -2 in the IG (95% confidence interval [CI] -2.75 to -1.31, p<0.001) and -0.88 (95% CI -1.43 to -0.33, p=0.003) in the CG, with a baseline-adjusted between-group difference of -1.31 ± 0.4 (95% CI -2.1 to -0.53; p=0.002). Pain at the 12-week follow-up visit remained significantly below baseline values in the IG. Disease activity and functional capacity showed statistically and clinically meaningful improvement after intervention but were not significant at the 12-week follow up. TNF and IL-6 levels changed significantly in the IG. Eighteen of 31 (58%) patients of the IG reduced or discontinued analgesics at the 12-week follow-up. No WBC-related side effects were reported.

Conclusion

WBC in RA reduces pain and disease activity significantly and in a clinically meaningful manner, resulting in a reduction of analgesics. These effects are potentially based on a change in cytokine levels.

Key words

rheumatoid arthritis, whole-body cryotherapy, physical therapy, cytokines, disease activity

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Introduction

Cryotherapy is a commonly used treatment concept not only in sports but also in treating inflammatory arthritis, in particular for rheumatoid arthritis (RA) (1). It is most commonly used as a local treatment of a single inflamed joint (2). Explanations for its clinically beneficial effects, especially on pain, are emerging. For example, local cryotherapy has been found to downregulate interleukin (IL) -6 expression *in vitro* and IL-6, IL-17A, and IL-1β gene expression levels in an adjuvant-induced arthritis rat model (3). Moreover, local cryotherapy reduced IL-6 and IL-1β synovial protein levels in human knee arthritis that was mainly due to microcrystal-induced arthritis (4). In addition, different application forms of local cryotherapy decreased disease activity and tumour necrosis factor (TNF) α levels in RA patients (5).

RA is a chronic inflammatory autoimmune disease that primarily causes synovitis and joint destruction and thus leads to progressive disability (6). Approximately 0.5 to 1% of the general population is affected by RA (7). As RA often affects more than a single joint, the concept of whole-body cryotherapy (WBC) is attractive as an adjuvant treatment in flares or in addition to pharmacological treatment. WBC was developed in Japan in the late 1970s and has been used in Europe since the mid-1980s (8). Nowadays, it is often used in rehabilitation (9), but many commercial providers (10) also offer WBC treatment sessions that can be purchased and used individually. Beneficial effects of WBC are advertised by these commercial providers. Although the advertised effects in healthy individuals for regenerative purposes might hold promise, the clinical evidence regarding real effects in RA patients is scarce. Thus far, WBC has been compared to different application forms of local cryotherapy (8, 11), it has been evaluated at different freezing temperatures (8, 11), and it has been compared to different physical therapy (PT) and rehabilitation programmes and modalities in RA patients (9, 12, 13). However, no randomised controlled trial to date has evaluated the effects of WBC compared with placebo or no treatment in RA patients.

Therefore, the present randomised controlled trial investigated the effect of WBC on pain, disease activity, and distinct clinical and molecular parameters versus no treatment in RA patients.

Methods

Participants

Eligible patients were 18 years or older, had RA fulfilling the 2010 American College of Rheumatology (ACR) or European League Against Rheumatism (EULAR) classification criteria (14), had active disease according to an 28-joint disease activity score (DAS28) (15, 16) >3.6 (17) or pain level >5 on a numerical rating scale (NRS) and a DAS28 >3.2 (18), received stable pharmacological treatment for longer than 3 months before the trial, and were about to begin a 16-day multimodal rheumatologic complex treatment (MRCT) (19). Exclusion criteria were a body weight over 120 kg, intolerance to cold, any contraindication to cryotherapy (*e.g.* unstable coronary disease), acute infection during the trial, and a change in pharmacological treatment (glucocorticosteroids and/or in any sort of disease-modifying anti-rheumatic drug [DMARD]) or non-pharmacological treatment (*e.g.* PT) 4 weeks prior to study start or during the trial. RA patients receiving biological DMARDs were excluded. Furthermore, RA patients with a medical history of (secondary) fibromyalgia were excluded.

Outcomes and assessment

The primary endpoint was a difference between groups concerning a change in pain measured on an NRS (0 = no pain, 10 = worst pain) at discharge after the last WBC intervention (6 applications in 14 days at -130°C for 3 min) or following 16-day MRCT in an inpatient setting, adjusted for baseline measurement. Secondary outcomes were assessed at discharge and after 12 weeks of discontinued WBC treatment at the 12-week follow-up visit. Effects of WBC were evaluated based on i) disease activity measured by the DAS28 using the erythrocyte sedimentation rate (ESR), ii) functional capacity measured by

the Health Assessment Questionnaire - Disability Index (HAQ), iii) serum levels of pro-inflammatory (IL-6 and TNF-α) and anti-inflammatory (IL-10) cytokines, and iv) use of analgesics (start/stop/reduction/increase/continuation/alteration in non-steroidal anti-inflammatory drugs, metamizole, opioids, or cannabinoids).

The DAS28 measures disease activity in RA and is a composite score consisting of tender and swollen joint counts of 28 joints, ESR (used in this study), and the patient's assessment of disease activity. The score ranges from 0 to 10, with scores of 3.2 or less considered low disease activity and scores below 2.6 considered remission (15, 16). The minimally clinically important improvement (MCII) of the DAS28 is considered to be -1 (20).

The HAQ measures physical function and disability and assesses 8 functional categories (dressing and grooming, getting up, eating, walking, hygiene, reach, grip, and other activities), with scores ranging from 0 (no disability) to 3 (completely disabled). A decrease of 0.22 - 0.25 in the HAQ score is considered to be an MCII (21, 22).

Randomisation and blinding

Participants were randomly assigned in a 1:1 ratio to the intervention group (IG; WBC treatment) or control group (CG; no treatment) using block randomisation. Participants were not blinded. Treatment was delivered in an inpatient setting. The IG and CG were situated on different wards and were not paired for any group treatment to avoid contact. Furthermore, participants were told not to talk about the intervention. Investigators assessing effects and calculating disease activity scores were blinded.

Study procedures

Characteristics and baseline values were assessed at inclusion prior to the start of the 16-day MRCT. Outcomes were assessed after the intervention at the 16-day MRCT discharge and at a 12-week follow-up visit.

WBC treatment consisting of 6 sessions at -130° C using a cryosauna, "SPACE CABIN" (~230 V, 50 Hz, serial number: 1050, year of manufacture 2013) from Cryomed s.r.o., Slowakia (see Supplementary Fig. S1). WBC sessions were begun on the first day of MRCT and were repeated every third day. The therapy was administered to participants wearing bathing suit/underwear and warm socks. Fingers were placed under the armpits during the treatment to avoid frost damage. Temperatures between -110 and -170°C could be applied; in this study, a fixed temperature of -130°C was selected. The first session was set at 90 sec, the second at 120 sec, and from the third session onwards a time of 180 sec (3 min) was set.

The study used ELISA to detect changes in IL-6, IL-10, and TNF-α levels after the intervention (at discharge) and after 3 months, at the 12-week follow-up visit. Serum was centrifuged at 3,500 rpm at 15°C for 10 min, and plasma was centrifuged at 2,850 rpm at 4°C for 15 min. The sample aliquots were stored at -80°C until further use. Cytokine levels (IL-6, IL-10, TNF-α) were measured in sera using Quantikine® ELISA kits (R&D Systems) according to the manufacturer's instructions. Optical readings were taken with the SUNRISE (TECAN) reader system at 450 nm.

All patients underwent 16 days of MRCT, which is a special German multimodal treatment programme with a strong emphasis on PT. In order to achieve comparability and reproducibility for the purpose of this study, we defined a framework of PT modalities within the limits of legal and reimbursement requirements that included PT, occupational therapy, pain management, and behavioural therapy. It was tailored to RA patients and was applied to all study participants. The 16-day MRCT (14 days of treatment, with no treatment on Sundays) consisted of 755 min (12 h 35 min) of treatment per 7 treatment days (a total of 1510 min) in an inpatient setting. Twenty-eight PT sessions of different PT modalities had to be performed per 7 treatment days (for a minimum of 56 sessions). The MRCT programme started on the day of admission after medical examination. Patients were discharged one day after completion of the MRCT programme. In detail, every patient received 10 PT sessions (25 min each with a focus on joint function), 6 sessions of respiratory exercises (25 min each with a focus on thoracic mobility), 6 balneotherapy sessions (underwater exercise therapy, 25 min each with a focus on exercise and joint mobility), 6 massage sessions (25 min each with a focus on releasing muscle tension), 6 sessions with hot packs (20 min each after massage to further release muscle tension), 8 sessions of ergotherapy (30 min each with a focus on joint function), 6 sessions of progressive muscle relaxation (30 min each with a focus on pain reduction), and 6 sessions of electrotherapy (30 min to either reduce swelling or to promote relaxation). In addition, each participant received two 45-min educational sessions on RA.

Sample size

A sample size of 27 in each group was calculated to have a power of 90% to detect a large standardised effect size of 0.9 using a two-group t-test with a two-sided significance level of 5%. Anticipating a dropout rate of 15%, we aimed to recruit 32 patients per group. Sample size calculations were performed using nQuery 8.

Statistics

Population descriptives are summarised using mean and standard deviation (SD) and percentages of occurrence. Treatment effects are reported with standard error (SE) and 95% simultaneous confidence intervals (95% CI), as appropriate. Differences in outcomes between groups at discharge and follow-up were assessed by linear regression, with baseline observation as covariate. Differences in analgesic usage were analysed by Chi-squared test. Patients were analysed as randomised (intention-to-treat). Calculations were performed using R version 4.0.2.

Ethics

The study protocol was approved by the local ethics committee of the Faculty of Medicine of the Justus-Liebig-University Gießen (vote no. 09/14). The study complied with Good Clinical Practice guidelines and Declaration of Helsinki principles. All patients provided written informed consent.

Results

Between July 01, 2014, and January 01, 2016, 81 RA patients undergoing a 16-day MRCT were assessed for eligibility, of whom 17 were excluded. A total of 64 patients were enrolled and randomly assigned in a 1:1 ratio to the IG (WBC treatment) or CG (no treatment). 56 patients (IG: 31 patients, CG: 25 patients) completed the trial and were analysed (Fig. 1).

Baseline patient and disease characteristics are shown in Table I. The mean age in the IG was 59 years and in the CG 55 years. Patients in both groups had active disease with a mean DAS28 of 4.8 in the IG and 4.5 in the CG, respectively. Pain levels based on the NRS were high and comparable in the two treatment arms, with 5.0 in the IG and 5.4 in the CG.

The main outcome in this study was met, with a difference in pain (NRS) between groups of (mean ± SE) -1.31±0.4 (95% CI -2.1 to -0.53, p=0.002) in favour of the IG (Fig. 2). Patients in both groups experienced a significant decrease in pain levels: for the IG this was -2±0.3 (95% CI -2.75 to -1.31, p<0.001), thus also meeting the MCII for a change in pain levels, and for the CG this was -0.88±0.27 (95% CI -1.43 to -0.33, p=0.003). At the 12-week follow-up visit the IG still had significantly reduced pain compared to baseline (-1.35, 95% CI -2.18 to -0.53, p=0.002), although a significant difference between treatment groups was lacking (Estimate -1.0; 95% CI -2.12 to 0.13, p=0.09) (Suppl. Table S1).

There was a significant difference in disease activity (DAS28) between groups after the intervention (Estimate -0.67; 95% CI -1.31 to -0.02, p=0.04) but not at the 12-week follow-up visit (Estimate -0.44; 95% CI -1.17 to 0.28, p=0.24) (Fig. 2). However, the DAS28 of the IG was still significantly reduced compared to baseline values at the 12-week follow-up visit (Estimate -0.82; 95% CI -1.36 to -0.28; p=0.004). Patients in the CG experienced no statistically significant improvement in disease activity (Suppl. Table S1).

Functional capacity and disability assessed by the HAQ were significantly improved in the IG compared to the CG after the intervention but not at the 12-week follow up visit (Estimate -0.21; 95% CI -0.35 to -0.07, p=0.003 and Estimate -0.24; 95% CI -0.49 to 0.006, p=0.06, respectively) (Fig. 2). In comparison to the IG, the CG did not show a statistically significant improvement in functional capacity and disability (Suppl. Table S1).

Serum cytokine levels of pro-inflammatory cytokines IL-6 and TNF-α were significantly reduced in the IG af-

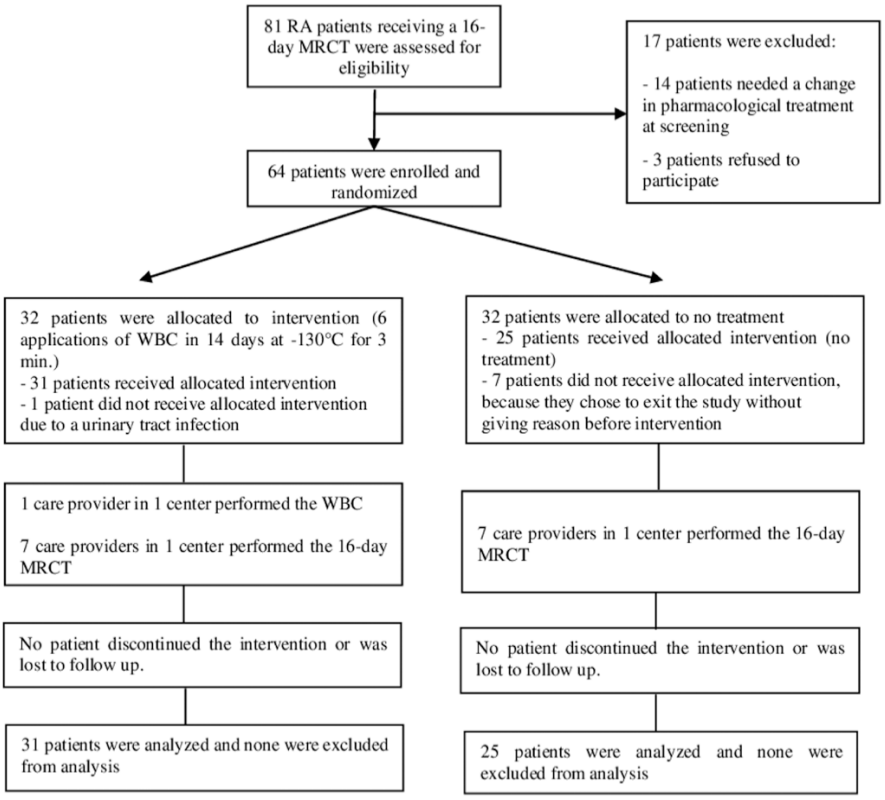

Fig. 1. Trial enrolment according to the CONSORT statement for randomised trials of non-pharmacologic treatments (23).

Table I. Baseline patients and disease characteristics.

	Intervention Group (n=31)	Control Group (n=25)
Age [years]	59.5 ± 5.7	55.1 ± 17
Sex [n (%)]		
female	25 (80%)	18 (72%)
male	6 (19%)	7 (28%)
RA duration [years]	3.2 ± 4.5	3.0 ± 5.0
RF and/or anti-CCP positive [n (%)]	21 (68%)	16 (65%)
Disease duration [years]	4.5 ± 3.2	4.8 ± 4.3
Concurrent csDMARD use [n (%)]	31 (100%)	25 (100%)
Concurrent methotrexate use [n (%)]	26 (84%)	20 (80%)
Concurrent oral steroid use [n (%)]	25 (81%)	22 (88%)
Steroid dose [mg/day]	6.6 ± 2.2	6.5 ± 2.4
Pain level [NRS]	5 ± 2.1	5.4 ± 2.3
HAQ	1 ± 0.6	1.24 ± 0.5
ESR [mm]	17 ± 11	18 ± 13
DAS28	4.8 ± 1.5	4.5 ± 1.3

Data are mean ± standard deviation, unless otherwise indicated.
HAQ: Health Assessment Questionnaire; ESR: erythrocyte sedimentation rate; DAS28: 28 joint disease activity score; NRS: numeric rating scale (0 = no pain, 10 = outmost pain); CCP: cyclic citrullinated peptides; RA: rheumatoid arthritis; RF: rheumatoid factor; csDMARD: conventional synthetic disease-modifying anti-rheumatic drug.

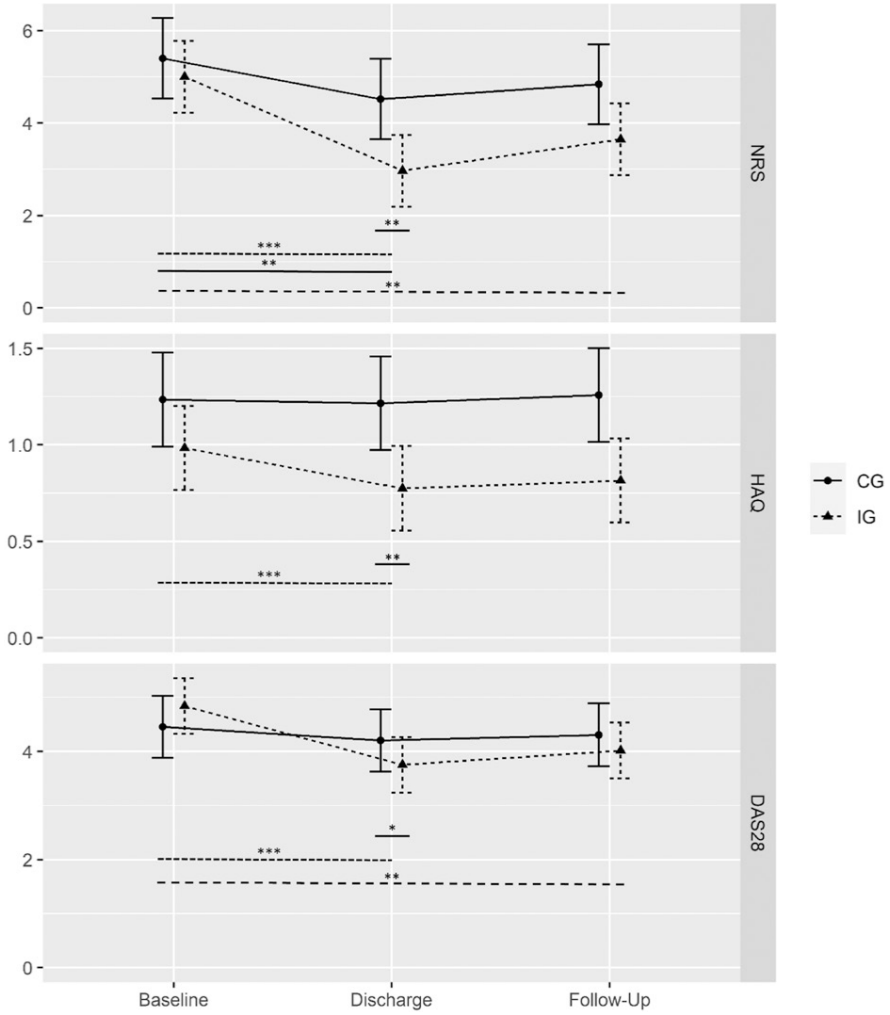

Fig. 2. Trial outcomes. Course of pain levels (NRS), disability (HAQ), and disease activity (DAS28) of the intervention group (IG) and the control group (CG) during the trial (from baseline to discharge) and at the 12-week follow-up visit. Baseline-Adjusted significant group differences and differences between time points are depicted.
*p<0.05, **p<0.01, ***p<0.001).

ter the intervention and at the 12-week follow-up visit compared to baseline. However, differences between the IG and CG were not shown to be statistically significant (Suppl. Table S1). Serum cytokine levels of the anti-inflammatory cytokine IL-10 did not show statistically significant differences in the IG after intervention or at the 12-week follow-up visit, and there were no differences in the between-group comparison (Suppl. Table S1).

At baseline, 20 out of 25 (80%) patients in the CG and 22 out of 31 (71%) patients in the IG used analgesics. At the 12-week follow-up visit, 16 out of 25 (64%) (CG) and 16 out of 31 (52%) (IG) patients used analgesics. Nine out of 31 (29%) patients in the IG and 5 out 25 (20%) patients in the CG had stopped or reduced the use of their analgesics at the 12-week follow-up visit (Table II). Chi-squared tests for differences between IG and CG did not reveal significant differences, likely due to small sample sizes.

Discussion

To the best of our knowledge, this is the first study to evaluate the effect of WBC in patients with active RA in a randomised controlled trial setting that included a no-WBC-treatment group with a 12-week follow-up period. The main outcome was met with a significant difference in baseline-adjusted pain after the intervention of 1.31 NRS points *versus* the control group and with a clinically significant improvement in pain in the IG when comparing baseline to discharge values. Not only did the beneficial effects on pain due to WBC treatment persist, as patients in the IG experienced continuous and significantly lower pain levels at the 12-week follow-up visit compared to baseline, but functional capacity also showed a relevant improvement in the IG compared to the CG after the intervention and at the 12-week follow-up visit. Disease activity was significantly reduced in the IG after the intervention, with significantly lower disease activity at the 12-week follow-up visits than baseline. In addition, significantly altered cytokine levels were detectable in the IG both after the intervention and at the 12-week follow up as a potential explanation of the beneficial clinical effects of WBC treatment on RA. However, these differences were not

Table II. Analgesic usage over time.

	Intervention group (n=31)			Control group (n=25)		
Analgesic usage	Baseline	After intervention	12-week follow-up	Baseline	After intervention	12-week follow-up
None	9	14	15	5	7	9
Reduction		7	3		1	1
Constant	22	9	8	20	13	9
Increase		1	5		4	6

No WBC-related side effects were reported.

apparent in the between-group comparison.

The inclusion and exclusion criteria of the trial led to the inclusion of RA patients with active disease (17, 18) who were on conventional synthetic DMARD therapy. Instead of an increase in the use and intensity of pharmacological treatment, non-pharmacological therapy was begun in both groups. We compared the effects of cryotherapy together with a 16-day MRCT, which can reduce pain and disease activity in RA patients (19, 24). Since both groups were on MRCT, any additional improvements in the CG would also have been observed. Starting active background therapy at trial start is common: in the LUNAR trial, for example, rituximab was evaluated in the treatment of lupus nephritis just when all participants had begun mycophenolate therapy at study start (25). Furthermore, the study design is comparable to that of pharmacological trials in rheumatology assessing pharmacological therapies in RA patients with active disease who were on conventional synthetic DMARDs (*e.g.* methotrexate, analogous to MRCT here) plus verum (WBC) or placebo (no WBC) (26, 27).

The effects of WBC treatment were statistically and clinically significant over a 16-day period with only 6 WBC sessions applied at -130°C. Twelve weeks after WBC treatment, patients in the IG still experienced continuously lower pain levels compared to baseline, and 9 out of 31 (29%) of WBC-treated RA patients had reduced or stopped their use of analgesics. This is a highly beneficial additional clinical effect achieved with a single intervention (6 sessions of WBC at -130°C of maximally 3 min each). Thus, WBC seems to be a good and fast-acting therapy for patients with active RA. As there is no protocol for the correct amount and frequency of WBC therapy, 6 WBC sessions were chosen here based on a prior study reporting good effects in patients with fibromyalgia (28). Furthermore, we hypothesised that 6 WBC sessions can be relatively easily implemented in any outpatient setting, as WBC was shown to be a good addition to pharmacological therapy in a multimodal approach incorporating PT, which is advocated in the current guidelines (29). In this context, WBC could be used, for example, in daily practice in the setting of a newly begun pharmacological therapy to reduce pain and disease activity while waiting for pharmacological effects to settle in.

Cryotherapy, although its mode of action remains unclear, has been shown to affect cytokine levels (3-5). For example, local cryotherapy seems to mediate its effect by a down-regulation of joint and systemic IL-6 or IL-17 pathways and not the TNF-α pathway (30). As the effects of local and systemic therapy on cytokines are probably very different, serum levels of a number of cytokines were investigated further in our study. Only the IG showed statistically significant changes, with a reduction in TNF-α levels after the intervention and at the 12-week follow-up, although differences between IG and CG were not significant. The decline in TNF-α levels seems to have paralleled changes in clinical parameters such as the continuous reduction in pain and disease activity and the need for fewer analgesics; however, this was neither statistically tested nor proven. The serum levels of IL-6 and IL-10, additional disease-related pro- and anti-inflammatory cytokines, showed no significant change in either the IG or the CG. As included patients were on stable non-biological DMARD pharmacological therapy 4 weeks prior to study start and throughout the whole trial, the change in cytokine levels does not seem to have been pharmacologically induced. One explanation for this finding could be that pro-inflammatory cytokines like TNF-α, IL-1, and IL-6 not only play a central role in local rheumatic inflammatory processes but also influence nociception (31). Local nociceptive reactions involve peripheral polymodal nociceptors expressing glycoprotein 130, which plays a role in cytokine signaling (32, 33). In so-called inflammatory pain, there is an interaction and a certain balance between analgesic (including IL-1, -4, -10, and -13) and hyperalgesic (including bradykinin, prostaglandins, IL-1, -6, -8, and TNF-α) mediators. In the early stage, hyperalgesic mediators dominate while at the same time analgesically active cytokines are induced by the immune system (32, 33). A decrease of these mediators may lead to reduced depolarisation of the peripheral nociceptors due to reduced input from ascending neurons in the cortical pain matrix and therefore enhance a subsequent decrease in pain sensation.

Limitations

The main limitation is the study design, as the treatment arms were randomised but not blinded to treatment. Due to the nature of WBC (very cold) and its application (in a chamber), patient blinding is nearly impossible. Nonetheless, assessors evaluating effects and assessing disease activity were blinded, and we avoided between-group interaction by separating treatment groups physically and temporally and asking participants not to talk about the intervention. However, 7 of 8 (87%) dropouts occurred in the CG (before trial start), possibly due to disappointment of not receiving WBC. This may have introduced an attrition bias, further narrowing the effect of WBC. Due to inclusion criteria (active disease), WBC was evaluated during active MRCT therapy. Further evaluation in a trial without background treatment analogous to the procedures of pharmacological trials aimed at approval of a new drug would help to show the beneficial effects of WBC in the setting of an active background treatment compared to an approach without background treatment (34). In conducting such a trial, we would recommend a larger sample size to be able to further assess changes in DAS28 and cytokines more meaningfully.

Generalisability

The results showing beneficial effects of WBC in this study are consistent with previous work (8, 9, 11-13), albeit study design and hypothesis are not comparable. To the best of our knowledge, WBC was clinically evaluated in 5 studies thus far (8, 9, 11-13). Hirvonen *et al*. compared WBC at -110°C to WBC at -60ºC and to application of local cold air at -30ºC in RA patients and found that the decrease in pain was

greater treated with WBC at -110°C compared to the other treatment arms (11). In an additional study under similar conditions, Hirvonen et al. investigated the total antioxidative capacity of WBC, which was positively altered only in the WBC at -110°C treatment for a short duration (8). Gizinska *et al*. compared WBC (-110°C) integrated into a rehabilitation programme with a "traditional" rehabilitation programme in RA patients assessing pain, disease activity, and serum cytokine levels among other factors. No statistically significant differences were found, as RA patients in both arms experienced less pain and less disease activity with lower levels of IL-6 and TNF-α (13). Wojtecka-Lukasik *et al*. evaluated a change in histamine levels in RA and osteoarthritis patients treated with WBC alone (-140 to -160°C) or in combination with physiotherapy and found histamine levels in RA patients to be significantly changed in the WBC treatment arm (12). Ksiezopolska-Orłowska *et al*. compared the impact of two rehabilitation programmes on pain and disease activity amongst others in RA patients (9). A rehabilitation programme incorporating both WBC (-120°C) and local cryotherapy (-160°C) performed better than the rehabilitation programme without cryotherapy (neither local nor WBC) (9). On the backdrop of these studies (8, 9, 11-13), our study provides further supporting evidence for a beneficial effect of WBC treatment in RA patients suffering from pain and elevated disease activity.

Interpretation

WBC is an effective treatment approach for patients with active RA that leads to reduced pain and disease activity with prolonged effects after discontinued therapy.

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References

1. GUILLOT X, TORDI N, MOUROT L *et al*.: Cryotherapy in inflammatory rheumatic diseases: a systematic review. *Expert Rev Clin Immunol* 2014; 10: 281-94. https://doi.org/10.1586/1744666x.2014.870036
2. ALBRECHT K, ALBERT C, LANGE U, MULLER-LADNER U, STRUNK J: Different effects of local cryogel and cold air physical therapy in wrist rheumatoid arthritis visualised by power Doppler ultrasound. *Ann Rheum Dis* 2009; 68: 1234-5. https://doi.org/10.1136/ard.2008.096081
3. GUILLOT X, MARTIN H, SEGUIN-PY S *et al*.: Local cryotherapy improves adjuvant-induced arthritis through down-regulation of IL-6 / IL-17 pathway but independently of TNF-α. *PLoS One* 2017; 12: e0178668. https://doi.org/10.1371/journal.pone.0178668
4. GUILLOT X, TORDI N, LAHEURTE C *et al*.: Local ice cryotherapy decreases synovial interleukin 6, interleukin 1β, vascular endothelial growth factor, prostaglandin-E2, and nuclear factor kappa B p65 in human knee arthritis: a controlled study. *Arthritis Res Ther* 2019; 21: 180. https://doi.org/10.1186/s13075-019-1965-0
5. JASTRZĄBEK R, STRABURZYŃSKA-LUPA A, RUTKOWSKI R, ROMANOWSKI W: Effects of different local cryotherapies on systemic levels of TNF-α, IL-6, and clinical parameters in active rheumatoid arthritis. *Rheumatol Int* 2013; 33: 2053-60. https://doi.org/10.1007/s00296-013-2692-5
6. MCINNES IB, SCHETT G: The pathogenesis of rheumatoid arthritis. *N Engl J Med* 2011; 365: 2205-19. https://doi.org/10.1056/nejmra1004965
7. SMOLEN JS, ALETAHA D, BARTON A *et al*.: Rheumatoid arthritis. *Nat Rev Dis Prim* 2018; 4: 18001. https://doi.org/10.1038/nrdp.2018.1
8. HIRVONEN H, KAUTIAINEN H, MOILANEN E, MIKKELSSON M, LEIRISALO-REPO M: The effect of cryotherapy on total antioxidative capacity in patients with active seropositive rheumatoid arthritis. *Rheumatol Int* 2017; 37: 1481-7. https://doi.org/10.1007/s00296-017-3771-9
9. KSIĘŻOPOLSKA-ORŁOWSKA K, PACHOLEC A, JĘDRYKA-GÓRAL A *et al*.: Complex rehabilitation and the clinical condition of working rheumatoid arthritis patients: does cryotherapy always overtop traditional rehabilitation? *Disabil Rehabil* 2016; 38: 1034-40. https://doi.org/10.3109/09638288.2015.1060265
10. Startseite - Cryopoint n.d. https://cryopoint.de/ (accessed 11 January 2021).
11. HIRVONEN HE, MIKKELSON MK, KAUTIAINEN H, POHJOLAINEN TH, LEIRSALO-REPO M: Effectiveness of different cryotherapies on pain and disease activity in active rheumatoid arthritis. A randomised single blinded controlled trial. *Clin Exp Rheumatol* 2006; 24: 295-301.
12. WOJTECKA-LUKASIK E, KSIEZOPOLSKA-ORLOWSKA K, GASZEWSKA E *et al*.: Cryotherapy decreases histamine levels in the blood of patients with rheumatoid arthritis. *Inflamm Res* 2010; 59: 253-5. https://doi.org/10.1007/s00011-009-0144-1
13. GIZIŃSKA M, RUTKOWSKI R, ROMANOWSKI W, LEWANDOWSKI J, STRABURZYŃSKA-LUPA A: Effects of whole-body cryotherapy in comparison with other physical modalities used with kinesitherapy in rheumatoid arthritis. *Biomed Res Int* 2015; 2015: 1-7. https://doi.org/10.1155/2015/409174
14. ALETAHA D, NEOGI T, SILMAN AJ *et al*.: 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010; 69: 1580-8. https://doi.org/10.1136/ard.2010.138461
15. PREVOO MLL, VANT' HOF MA, KUPER HH, VAN LEEUWEN MA, VAN DE PUTTE LBA, VAN RIEL PLCM: Modified disease activity scores that include twenty-eight-joint counts development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995; 38: 44-8. https://doi.org/10.1002/art.1780380107
16. WELLS G, BECKER J-C, TENG J *et al*.: Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythr. *Ann Rheum Dis* 2009; 68: 954-6. https://doi.org/10.1136/ard.2007.084459
17. ALETAHA D, WARD MM, MACHOLD KP, NELL VPK, STAMM T, SMOLEN JS: Remission and active disease in rheumatoid arthritis: Defining criteria for disease activity states. *Arthritis Rheum* 2005; 52: 2625-36. https://doi.org/10.1002/art.21235
18. PREVOO ML, VAN GESTEL AM, VAN'T HOF MA, VAN RIJSWIJK MH, VAN DE PUTTE LB, VAN RIEL PL: Remission in a prospective study of patients with rheumatoid arthritis. American Rheumatism Association preliminary remission criteria in relation to the disease activity score. *Br J Rheumatol* 1996; 35: 1101-5. https://doi.org/10.1093/rheumatology/35.11.1101
19. KLEMM P, HUDOWENZ O, ASENDORF T, MÜLLER-LADNER U, LANGE U, TARNER IH: Multimodale rheumatologische Komplexbehandlung bei rheumatoider Arthritis – eine monozentrische Retrospektivanalyse. *Z Rheumatol* 2019; 78: 136-42. https://doi.org/10.1007/s00393-019-0593-z
20. WARD MM, GUTHRIE LC, ALBA MI: Clinically important changes in individual and composite measures of rheumatoid arthritis activity: thresholds applicable in clinical trials. *Ann Rheum Dis* 2015; 74: 1691-6. https://doi.org/10.1136/annrheumdis-2013-205079
21. WELLS GA, TUGWELL P, KRAAG GR, BAKER PRA, GROH J, REDELMEIER DA: Minimum important difference between patients with rheumatoid arthritis: the patients perspective. *J. Rheumatol* 1993; 20: 557-60.
22. REDELMEIER DA: Assessing the Clinical Importance of Symptomatic Improvements. Arch Intern Med 1993;153:1337.
23. BOUTRON I, ALTMAN DG, MOHER D, SCHULZ KF, RAVAUD P: CONSORT statement for randomized trials of nonpharmacologic treatments: a 2017 update and a CONSORT extension for nonpharmacologic trial abstracts. *Ann Intern Med* 2017; 167: 40. https://doi.org/10.7326/m17-0046

24. KLEMM P, PREUSLER P, HUDOWENZ O *et al*.: Effects of multimodal rheumatologic complex treatment in patients with rheumatoid arthritis: a monocentric prospective study. *Clin Exp Rheumatol* 2022; 40(7): 1343-51. https://doi.org/10.55563/clinexprheumatol/lmbdlm
25. ROVIN BH, FURIE R, LATINIS K *et al*.: Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: The lupus nephritis assessment with rituximab study. *Arthritis Rheum* 2012; 64: 1215-26. https://doi.org/10.1002/art.34359
26. BURMESTER GR, KREMER JM, VAN DEN BOSCH F *et al*.: Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2018; 391:2 503-12. https://doi.org/10.1016/s0140-6736(18)31115-2
27. GENOVESE MC, KALUNIAN K, GOTTENBERG J-E *et al*.: Effect of filgotinib versus placebo on clinical response in patients with moderate to severe rheumatoid arthritis refractory to disease-modifying antirheumatic drug therapy. *JAMA* 2019; 322: 315. https://doi.org/10.1001/jama.2019.9055
28. KLEMM P, BECKER J, AYKARA I *et al*.: Serial whole-body cryotherapy in fibromyalgia is effective and alters cytokine profiles. *Adv Rheumatol* 2021; 61: 3. https://doi.org/10.1186/s42358-020-00159-z
29. RAUSCH OSTHOFF A-K, NIEDERMANN K, BRAUN J *et al*.: 2018 EULAR recommendations for physical activity in people with inflammatory arthritis and osteoarthritis. *Ann Rheum Dis* 2018; 77: 1251-60. https://doi.org/10.1136/annrheumdis-2018-213585
30. GUILLOT X, MARTIN H, SEGUIN-PY S *et al*.: Local cryotherapy improves adjuvant-induced arthritis through down-regulation of IL-6/IL-17 pathway but independently of TNFα. *PLoS One* 2017; 12: e0178668. https://doi.org/10.1371/journal.pone.0178668
31. RITTNER HL, BRACK A, STEIN C: Pain and the immune system: friend or foe? *Anaesthesist* 2002; 51: 351-8. https://doi.org/10.1007/s00101-002-0306-9
32. BOETTGER MK, HENSELLEK S, RICHTER F *et al*.: Antinociceptive effects of tumor necrosis factor α neutralization in a rat model of antigen-induced arthritis: Evidence of a neuronal target. *Arthritis Rheum* 2008; 58: 2368-78. https://doi.org/10.1002/art.23608
33. KULKARNI B, BENTLEY DE, ELLIOTT R *et al*.: Arthritic pain is processed in brain areas concerned with emotions and fear. *Arthritis Rheum* 2007; 56: 1345-54. https://doi.org/10.1002/art.22460
34. VOLLENHOVEN R, TAKEUCHI T, PANGAN AL *et al*.: Efficacy and safety of upadacitinib monotherapy in methotrexate-naive patients with moderately-to-severely active rheumatoid arthritis (SELECT-EARLY): a multicenter, multi-country, randomized, double-blind, active comparator-controlled trial. *Arthritis Rheumatol* 2020; 72: 1607-20. https://doi.org/10.1002/art.41384