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Original Article

Efficacy of whole-body cryotherapy in the treatment of chronic low back pain: Quasi-experimental study

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ABSTRACT

Study design: Single arm, quasi-experimental study design.
Background: To describe the effects of whole-body cryotherapy on pain, disability, and serum inflammatory markers in patients with chronic low back pain.
Methods: A quasi-experimental trial was performed on adult patients between 18 and 65 years with chronic low back pain. After obtaining informed consent, participants underwent 20 sessions of whole-body cryotherapy (at −160 °C) during a 5-week time span. Patient reported pain and disability measures (Pain Numerical Rating Scale [PNRS], Oswestry Disability Index [OSI], and Roland Morris Questionnaire [RMQ]) were obtained at each of the twenty sessions. Blood samples were obtained to analyze serum inflammatory markers at baseline, 10th and 20th session.
Results: Forty-one participants were included in the study. A significant decrease was observed between the initial and final PNRS, ODI, and RMQ scores ($p < 0.001$). A significant reduction in the PNRS was found after 4 sessions of whole-body cryotherapy ($p < 0.001$). We observed decreasing values of pro-inflammatory serum marker IL-2 ($p = 0.046$) and a significant increase in the anti-inflammatory serum marker IL-10 ($p = 0.003$). No adverse events were reported during the study.
Conclusions: Whole-body cryotherapy is an effective therapy for pain and disability treatment in chronic low back pain. It also produces changes in serum markers of inflammation, decreasing pro-inflammatory markers and increasing anti-inflammatory markers.

1. Introduction

Low back pain (LBP) is a condition with considerably high prevalence among the general population where at least 80% of people will suffer an episode of LBP during their lifetime [1,2]. It is one of the most common reasons for physician visits and is also associated to high costs related to healthcare and lost work days, all of which make it a public health problem [1–3]. It is classified according to symptoms duration, etiology, presence of neurological symptoms, and corresponding radiological abnormalities. According to pain duration, it is classified as acute (less than 4 weeks), subacute (4–12 weeks) and chronic (more than 12 weeks) [3]. Moreover, according to its characteristics it is also classified into specific, mainly due to systemic or visceral conditions, or non-diagnosed LBP which is the most common classification and has a mechanical etiology [1].

Cold therapy is a commonly used therapeutic procedure used to reduce pain in inflammatory musculoskeletal diseases and injuries. Whole Body Cryotherapy (WBC) consists of the exposure of the human body to extremely cold dry air; it is performed in a partial cryocabin, which is an open tank where the subject is exposed to temperatures ranging from −110 °C to −195 °C, except for the head

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and neck. This technique was first developed by Yamauchi in 1979 and its technology is based on cooling the cabin by spraying nitrogen inside it. An important safety feature is the exclusion of the head from the cabin to prevent breathing nitrogen [4].

WBC was first used in the management of rheumatological diseases such as rheumatoid arthritis [4–7], fibromyalgia [4,8], and ankylosing spondylitis [4,9], and it has also been described to be used for the treatment of depression and anxiety syndromes [4,10]. Furthermore, it is a popular practice among high performance athletes for enhancing muscle recovery after exercise [4,11,12].

The mechanism by which pain and inflammation are relieved after WBC treatment is not described yet. It has been hypothesized to be related to cold-induced analgesia, lower levels of oxidative stress, and inflammation. A decrease in pro-inflammatory serum markers and an increase in anti-inflammatory substances, however, have been reported [13–15]. In chronic LBP, a double blind randomized controlled trial that included 10 sessions of cryotherapy in a cryochamber at −67 °C concluded that it was not superior to sham cryotherapy at −5 °C, even though pain improvement was observed for both groups [16]. Another clinical trial in a similar population observed a decrease in pain after repeated exposure to WBC during a 3-week span [17].

Although some promising results have been observed, there is currently not enough evidence to recommend cold therapy for treating LBP [3]. Therefore, the objective of this study was to describe the effects of WBC on pain, disability, and serum inflammatory markers in patients with chronic LBP by performing a clinical trial.

2. Material and methods

2.1. Study design and setting

This was a quasi-experimental study design performed at the Department of Sports Medicine and Rehabilitation of a medical institution located at Monterrey, Mexico to describe the effect of WBC on pain, disability and serum inflammatory markers among participants with chronic LBP.

2.2. Eligibility criteria

Adult participants between 18 and 65 years of age with a chronic LBP diagnosis (lasting more than 12 weeks) of mechanical etiology reporting a Pain Numeric Rating Scale (PNRS; 0–10) over 5 were considered for inclusion. A Magnetic Resonance Imaging (MRI) and two-view spine radiographies were performed on each participant to exclude other etiologies (such as infections, tumors, osteoporosis, rheumatoid arthritis, fractures or inflammatory processes). Potential participants with any of the following conditions were excluded: cardiovascular diseases, medical conditions that could be exacerbated by exposure to cold temperature, neurological diseases, and drug and alcohol abuse, among other conditions deemed appropriate for exclusion.

2.3. Intervention description

Each participant was exposed to a total of 20 sessions of WBC at −160 °C for 3 min in a cryocabin (Chillout, CRYO-B, Guadalajara, Mexico) during a 5-week span with a frequency of 4 sessions per week. Before each session, PNRS was obtained, and blood pressure and pulse rate were measured. During the procedure, individuals wore minimal clothing, gloves, and dry shoes and socks to reduce the risk of cold-related injuries, they were also provided with instructions to prevent inhaling nitrogen.

2.4. Measurements

The patients were evaluated on 3 occasions, before the first session, after the tenth session, and 24 h after they took the last session. The PNRS, Oswestry Disability Index (ODI) and Roland–Morris Questionnaire (RMQ) were applied in the aforementioned sessions (the PNRS was also applied after each of the WBC sessions in order to determine at what exact point there was a significant decrease in pain); these questionnaires are reported by the patient and measure the severity of symptoms. The PNRS ranges from 0 to 10 (increasing score translates into increasing severity of pain). The ODI has become one of the principal condition-specific outcome measures used in the management of spinal disorders. It has 10 sections. For each section of six statements the total score is 5; if the first statement is marked, the score is 0; if the last statement is marked, it is 5. Intervening statements are scored according to rank. If more than one box is marked in each section, the highest score is taken. If all 10 sections are completed, the score is calculated as a percentage of 50 total points. If one section is missed, it is expressed as a percentage of the only available points. It is suggested to round the percentage to a whole number for convenience [18]. The RMQ is a widely used validated scale for measuring disability. It is simple, fast, and can be filled out by the patient. It consists of 24 items, which reflect limitation in different activities of daily living attributed by the patient to LBP. The patient must mark each item that applies to his or her current status. Scoring is also simple and fast. Each checked item receives a score of 1, so scores range between 0 (no disability caused by LBP) and 24 (the maximum possible disability) [19]. Blood samples were obtained at each evaluation to evaluate the following inflammation parameters: interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor-alpha (TNF-α) and C-reactive protein (CRP) (based on results of previous studies and reviews that have shown abnormal levels of these cytokines in patients with chronic LBP) [20,21].

Participants were followed-up by telephone one month after the last WBC session in order to check any adverse event and level of pain.

2.5. Sample size and statistical analysis

Sample size was calculated by estimating the mean pain decrease in LBP after WBC treatment as a main outcome. A standard deviation of 2 in pain score was determined by consensus and t-distribution was employed to estimate sample size in an infinite population size, thus the study would require a sample size of 43 to estimate a mean 95% confidence interval and a precision of 0.6. Data were analyzed using IBM SPSS version 20 (SPSS, Inc., Armonk, NY). Descriptive statistics were obtained and the Kolmogorov–Smirnov test was performed to characterize the distribution of PNRS, ODI, RMQ and laboratory values, which is presented in terms of mean and standard deviation (SD) or median and interquartile range (IQR) The Friedman test was employed to analyze the difference between PNRS, ODI, and RMQ score ranges at the three time points (baseline, 10th session, 20th session). We determined a confidence interval of 95% and considered a p value < 0.05 to be statistically significant. The PNRS scores measured before every session were compared with the Friedman test. A post hoc Bonferroni test was performed to compare PNRS estimated marginal means between single sessions and between 5-session intervals. We applied the same analysis to laboratory workup of IL-1b, IL-2, IL-6, IL-10, TNF-α and CRP.

2.6. Ethical disclosures

The trial was approved by the Ethical Committee of the University Hospital and School of Medicine of the UANL. Informed

consent was obtained from all participants. All procedures were done according to the International Conference of Harmonisation Guideline for Good Clinical Practice.

3. Results

3.1. Baseline characteristics

The total initial study population of 41 participants completed the intervention and is included in the final analysis. Mean age of participants was 37.3 (±12) years and 51.2% were female. Mean BMI of the sample was 28.8 (±6). Other baseline characteristics can be observed in Table 1. No adverse events related to the intervention were reported by patients during the study period. One month after the last session, all participants reported an PNRS score <3 and none reported any additional adverse event.

3.2. Change in patient reported measurements

A statistically significant decrease between the baseline and final session (20th session, 5 weeks after baseline) was observed for each of the patient reported measurements (p, <0.0001). The PNRS decreased from a median of 7 (IQR 6–8) to 3 (IQR 1–4) (Fig. 1). Similarly, the ODI score decreased from a median of 28 (IQR 21.2–37.5) to 12 (7.29.5) (Fig. 2) and 9 (7–14) to 4 (1–8) for the RMQ (Fig. 3). When comparing the three measurements, statistically significant decreases in the measurements were observed for the values of PNRS, ODI, and RMQ scores ($p < 0.05$). After performing a post-hoc analysis for the PNRS measurement, we observed that a statistically significant decrease in pain was observed after the fourth WBC session (p, <0.0001).

Table 1
Description of anthropometric characteristics of the sample.

	Men	Women	Total
	n = 20	n = 21	n = 41
Age, years	35 ± 12	39.5 ± 12	37.3 ± 12
Height, cm	174.3 ± 7.4	160.4 ± 6.6	167.5 ± 9.87
Weight, kg	89.22 ± 21.1	72.0 ± 12.9	80.8 ± 19.4
Body Mass Index, kg/m^2	29.2 ± 6.6	28.4 ± 5.4	28.8 ± 6
Percentage Body Fat, %	27.85 ± 9.39	38.78 ± 9.45	33.31 ± 10.82

Values are mean ± standard deviation.

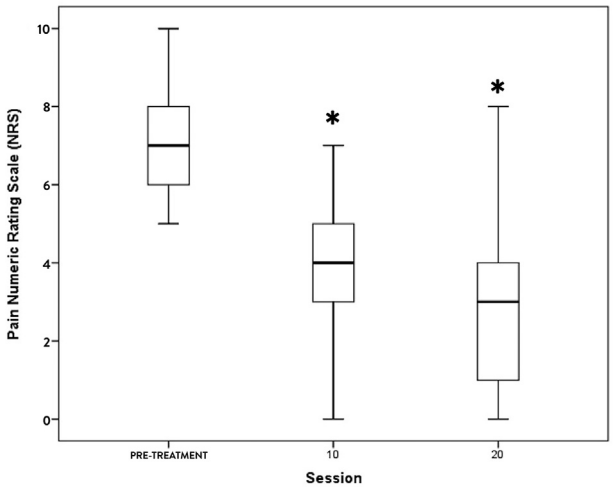

Fig. 2. ODI reduction during the trial. Disability scores measured before the first session, after the tenth session, and 24 h after the last WBC session (95% CI; $p < 0.0001$). * Significant differences.

3.3. Change in serum inflammatory markers

No statistically significant decreases were observed after twenty sessions of WBC with regard to IL-6, IL-1b, TNF-α, and CRP (Table 2). A statistically significant increase was observed for IL-10 (p, 0.003) whereas a decrease was observed in IL-2 levels (p, 0.046) (Table 2).

4. Discussion

In this trial, repeated exposure to extremely cold temperatures during 3 min produced a significant reduction of pain perception and other disability symptoms in patients with chronic LBP. The analgesic effect of WBC reached significant values at the end of the fourth session, and it accumulated along the latter sessions. Serum inflammatory markers also showed positive changes: declining values of IL-2 and augmented levels of IL-10 were observed as

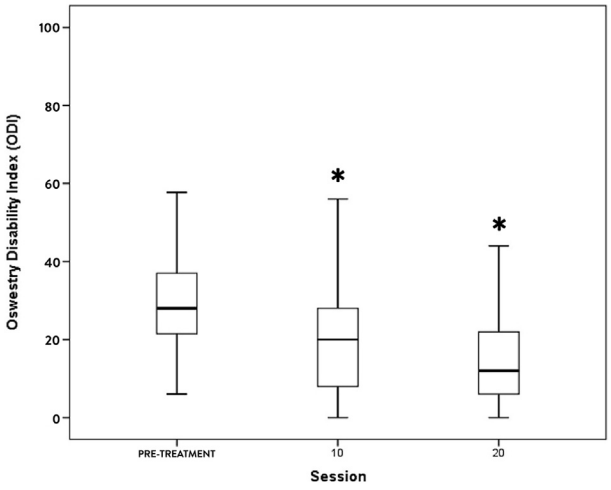

Fig. 1. PNRS reduction during the study. Pain scores measured before the first session, after the tenth session, and 24 h after the last WBC session (95% CI; $p < 0.0001$). * Significant differences.

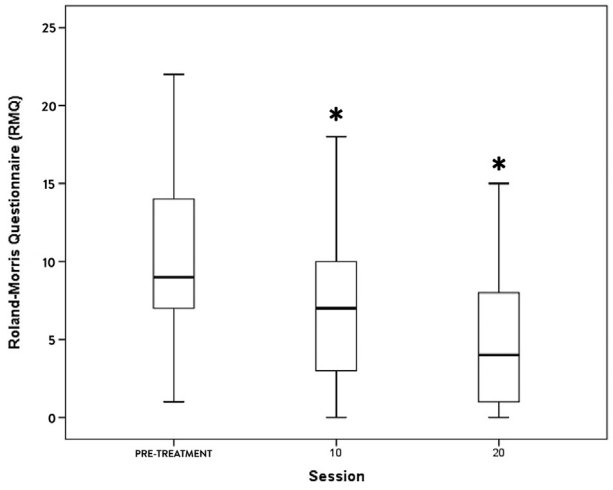

Fig. 3. RMQ reduction during the trial. Disability scores measured before the first session, after the tenth session, and 24 h after the last WBC session (95% CI; $p < 0.001$). * Significant differences.

Table 2
Analysis in serum inflammatory markers changes after WBC exposure.

Serum inflammatory markers	Session 1	Session 10	Session 20	p value
Il-2, pg/mL	10.39 (1.60–34.20)	4.56 (1.60–25.08)	3.30 (1.60–17.57)	**0.046**
Il-6, pg/mL	4.00 (4.000–103.59)	4.08 (4.00–71.30)	4.11 (4.00–65.44)	0.177
Il-10, pg/mL	2.00 (2.00–3.48)	3.48 (2.00–4.19)	4.28 (2.72–4.90)	**0.003**
Il-1b, pg/mL	0.50 (0.50–0.50)	0.50 (0.50–0.50)	0.50 (0.50–0.50)	0.818
TNF-α, pg/mL	5.26 (3.50–11.58)	6.09 (4.84–11.79)	5.68 (4.33–9.89)	0.736
CRP, mg/mL	2.92 (1.19–9.18)	1.78 (0.91–5.08)	2.25 (0.63–4.49)	0.236

Values in parentheses are interquartile range (IQR). The numbers in bold correspond to the values of "p" which obtained statistically significant results.

described in the literature [4,11]. These findings could imply that there are inflammatory mechanisms occurring in the pathogenesis of undiagnosed low back pain. We propose the hypothesis that there is a causal relationship between the significant improvement in the patient reported measurements and the clinical scores when administering cryotherapy sessions in patients with LBP and the increase in IL-10, which could lead to delimiting targeted therapies to this interleukin. However, we recognize that further studies are necessary to confirm this hypothesis.

There are studies that indicate an increase in the levels of anti-inflammatory cytokines (IL-2, IL-4 and IL-10,) and a decrease in them (CRP, IL-6, TNF-α, IL-8, and IL-1β) with respect to pain level [20]. However, to our knowledge, there are no previous studies that have compared the levels of these inflammatory mediators before and after treatment using WBC in patients with chronic LBP.

Chronic low back pain is a challenge for the physician. The fact that it is non-specific in most cases and represents a high economic burden compels them to search for efficient treatment options. Different treatment options have been investigated and there is a strong recommendation to initiate management with non-pharmacologic treatment in patients with acute and chronic LBP [3]. Furthermore, moderate quality evidence has been found for superficial heat in acute LBP, and for exercise, multidisciplinary rehabilitation, acupuncture, and mindfulness-based stress reduction in chronic LBP. Moreover, there is low quality evidence regarding low level laser therapy, electromyography biofeedback, motor control exercise, tai chi, yoga, massage, spinal manipulation, operant therapy, and cognitive behavioral therapy [3].

Cryotherapy has been used in the treatment of numerous conditions [4,5]. Its effects have been awarded to decreasing tissue temperature, reducing inflammation, and inducing analgesia and parasympathetic reactivation [11]; however, there is not enough evidence yet to recommend cold therapy for treating LBP [3]. In this study, we observed that a minimum number of sessions were necessary in order to observe a statistically significant drop in pain levels (four sessions). However, a benefit for continuing the treatment for the whole 20 sessions was observed, since a clinically important reduction of almost 50% was observed in both pain and disability scores.

Regarding Minimally Clinical Important Differences (MCID) for each score, the available literature describes a mean decrease of 2.4 for the PNRS, 5 for the RMQ, and 17 on the ODI questionnaire [22]. Although our data is reported in median values, decreases of 4, 5 and 16 were observed for each measurement, respectively.

The trial has some limitations that need to be highlighted. The main concern would be the lack of a control group; however, we performed this study with the intention of observing the preliminary efficacy of this therapy and its effect on both clinical and serological markers. Another limitation is the overweight that the patients presented. Similarly, there are different available cryotherapy modalities, therefore our findings should not be generalized to these other modalities. Future studies should be performed in order to establish if extreme cold temperatures offer any benefit, as well to analyze the cost-effectiveness of this therapy [11]. Another important limitation of this study is the inability to perform subgroup comparisons according to participants' age or other clinically relevant characteristics that would not be powered enough due to the sample size.

5. Conclusions

The results of this trial suggest that WBC could be recommended as an effective treatment for pain and disability in patients with chronic LBP due to the significant improvement in functional scores. We propose that there is a causal relationship between the administration of cryotherapy sessions and the increase in IL-10. Future studies with a control group of standard therapy should be performed in order to confirm whether WBC is an effective therapy when compared to other treatment modalities in chronic LBP.

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Research ethics and patient consent

All participants signed a written informed consent and were aware of the risks and benefits of the intervention.

Declaration of competing interest

The authors have no conflict of interests. Both funding sources did not intervene during any of the process of this study. Only authors participated in the preparation of the manuscript.

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References

[1] Golob AL, Wipf JE. Low back pain. Med Clin 2014 May;98(3):405–28.
[2] Patrick N, Emanski E, Knaub MA. Acute and chronic low back pain. Med Clin 2016 Jan;100(1):169–81.
[3] Qaseem A, Wilt TJ, McLean RM, Forciea MA. Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American college of physicians. Ann Intern Med 2017 Apr 4;166(7):514–30.
[4] Bouzigon R, Grappe F, Ravier G, Dugue B. Whole- and partial-body cryostimulation/cryotherapy: current technologies and practical applications. J Therm Biol 2016 Oct;61:67–81.
[5] Guillot X, Tordi N, Mourot L, Demougeot C, Dugué B, Prati C, Wendling D. Cryotherapy in inflammatory rheumatic diseases: a systematic review. Expet Rev Clin Immunol 2014 Feb;10(2):281–94.

[6] Jastrzabek R, Straburzyńska-Lupa A, Rutkowski R, Romanowski W. Effects of different local cryotherapies on systemic levels of TNF-alpha, IL-6, and clinical parameters in active rheumatoid arthritis. Rheumatol Int 2013 Aug;33(8):2053–60.
[7] Hirvonen HE, Mikkelsson MK, Kautiainen H, Pohjolainen TH, Leirisalo-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 May-Jun;24(3):295–301.
[8] Bettoni L, Bonomi FG, Zani V, Manisco L, Indelicato A, Lanteri P, Banfi G, Lombardi G. Effects of 15 consecutive cryotherapy sessions on the clinical output of fibromyalgic patients. Clin Rheumatol 2013 Sep;32(9):1337–45.
[9] Stanek A, Cholewka A, Gadula J, Drzazga Z, Sieron A, Sieron-Stoltny K. Can whole-body cryotherapy with subsequent kinesiotherapy procedures in closed type cryogenic chamber improve BASDAI, BASFI, and some spine mobility parameters and decrease pain intensity in patients with ankylosing spondylitis? BioMed Res Int 2015:1–11.
[10] Szczepańska-Gieracha J, Borsuk P, Pawik M, Rymaszewska J. Mental state and quality of life after 10 session whole-body cryotherapy. Psychol Health Med 2014;19(1):40–6.
[11] Bleakley C, Bieuzen F, Davison G, Costello J. Whole-body cryotherapy: empirical evidence and theoretical perspectives. Open Access J Sports Med 2014 Mar 10;5:25–36.
[12] Pournot H, Bieuzen F, Louis J, Fillard JR, Barbiche E, Hausswirth C. Time-course of changes in inflammatory response after whole-body cryotherapy multi exposures following severe exercise. PLoS One 2011;6(7):e22748.
[13] Banfi G, Melegati G, Barassi A, Dogliotti G, Melzi d'Eril G, Dugué B, Corsi M. Effects of whole-body cryotherapy on serum mediators of inflammation and serum muscle enzymes in athletes. J Therm Biol 2009 Feb;34(2):55–9.
[14] Lubkowska A, Szyguła Z, Chlubek D, Banfi G. The effect of prolonged whole-body cryostimulation treatment with different amounts of sessions on chosen pro- and anti-inflammatory cytokines levels in healthy men. Scand J Clin Lab Invest 2011 Sep;71(5):419–25.
[15] Ziemann E, Olek RA, Kujach S, Grzywacz T, Antosiewicz J, Garsztka T, Laskowski R. Five-day whole-body cryostimulation, blood inflammatory markers, and performance in high-ranking professional tennis players. J Athl Train 2012 Nov-Dec;47(6):664–72.
[16] Nugraha B. Effects of whole body cryo-chamber therapy on pain in patients with chronic low back pain: a prospective double blind randomised controlled trial. Eur J Phys Rehabil Med 2015 Apr;51(2):143–8.
[17] Giemza C, Matczak-Giemza M, De Nardi M, Ostrowska B, Czech P. Effect of frequent WBC treatments on the back pain therapy in elderly men. Aging Male 2015;18(3):135–42.
[18] Fairbank JC, Pynsent PB. The Oswestry disability Index. Spine 2000 Nov 15;25(22):2940–52.
[19] Kovacs FM, Llobera J, Gil del Real MT, Abraira V, Gestoso M, Fernández C, Primaria Group KA. Validation of the Spanish version of the roland-morris questionnaire. Spine 2002 Mar 1;27(5):538–42.
[20] Khan AN, Jacobsen HE, Khan J, Filippi CG, Levine M, Lehman Jr RA, Riew KD, Lenke LG, Chahine NO. Inflammatory biomarkers of low back pain and disc degeneration: a review. Ann N Y Acad Sci 2017 Dec;1410(1):68–84.
[21] Teodorczyk-Injeyan JA, Triano JJ, Injeyan HS. Nonspecific low back pain: inflammatory profiles of patients with acute and chronic pain. Clin J Pain 2019 Oct;35(10):818–25.
[22] Maughan EF, Lewis JS. Outcome measures in chronic low back pain. Eur Spine J 2010 Sep;19(9):1484–94.