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Does Cooling Therapy Improve Functional Mobility in Heat-Sensitive Adults Diagnosed With Multiple Sclerosis?

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not cooling therapy improves functional mobility in heat-sensitive adults diagnosed with MS.

STUDY DESIGN: Systematic review of three randomized controlled trials published between 2007 and 2011, all in the English language.

DATA SOURCES: Three randomized controlled trials were found using the PubMed/MEDLINE database.

OUTCOMES MEASURED: Functional mobility as measured by the Multiple Sclerosis Functional Composite (MSFC), postural control, exercise duration, walking speed, and timed up and go examinations.

RESULTS: In one study, Meyer-Heim, et al. demonstrated significant improvements with the experimental intervention on the 25-foot walk, 9-hole peg test, as well as the total MSFC, and no significant different on tests of postural sway and knee spasticity. In terms of exercise duration, Grahn, et al. found a significant improvement of 33% increase with cooling therapy. Finally, the study by Reynolds, et al. showed an improvement on the 6-minute walk test when comparing true cooling to the other tested conditions; on the 25-foot walk test and the timed up and go, true cooling was not associated with a significant improvement with regard to the other conditions.

CONCLUSIONS: The reviewed studies, representing the best evidence currently available, suggest the efficacy of cooling therapy as a well-tolerated method for improving functional mobility in heat-sensitive adults diagnosed with multiple sclerosis.

KEY WORDS: cooling, multiple sclerosis

INTRODUCTION

Multiple sclerosis (MS) refers to a condition in which there is an immune-mediated attack on the central nervous system (CNS). This attack damages the myelin on the neurons and causes sclerosis (scar tissue) that disrupts neural signal transmission.[1] The constellation of demyelinated neurons, degeneration, and sclerosis forms histopathologically characteristic inflammatory plaques.[2] This paper evaluates three randomized controlled trials (RCTs) comparing the efficacy of cooling therapy to placebo for improving functional mobility in adults with MS.

While the prevalence of MS has not been definitely established, it is thought to affect 400,000 people in the U.S. and 2.3 million globally.[3] The symptoms of fatigue, spasticity, and heat-sensitivity are interrelated and have a predominant role in determining the impact of MS on patients' activities of daily living.[4] Additionally, the disease presents a financial burden for patients and for society as a whole. The total cost of MS for the average patient is estimated to be $8528−$54,244 annually, and the condition costs the United States approximately $28 billion per year.[5] In fact, due to prescription drug costs and to the early onset of the disease, MS is the second costliest chronic condition (following congestive heart failure).[5]

The etiology of MS remains elusive; various triggers, such as viruses and environmental factors with coexisting immunodeficiency, are supported in the literature.[2] While the symptoms and disease course in MS vary on an individual basis, patients with relapsing-remitting multiple sclerosis (RRMS) are known to have elevated body temperature, even at rest.[1] In these patients, this state is associated with fatigue (general and physical), a phenomenon originally described by Wilhelm Uhthoff.[6]

Treatment of MS can include both symptomatic and disease-modifying components. The approach to therapy and specific medications chosen depend on the clinical picture as well as on the patient's preferences and input. Symptomatic treatment may include SSRIs (depression), muscle relaxants (spasticity), and anticholinergic agents (bladder urgency). Addressing the psychosocial impact of the disease is an essential component. Various disease-modifying treatments are approved for MS. These include interferons (e.g. IFN-ß1b [Betaseron]), immunomodulators (e.g. glatiramer acetate [Copaxone]), and monoclonal antibodies (e.g. natalizumab [Tysabri]).[7]

Because symptomatic treatment does not, as a rule, affect the course of the disease, patients may reasonably feel that potential adverse effects associated with these measures outweigh their benefits.[7] Furthermore, it seems logical that therapies capable of ameliorating symptoms without negatively impacting quality of life would be desirable for patients.

Since the observations of Uhthoff in 1890, exercise has been associated with transient worsening of MS symptoms in most patients (up to 80%). The etiology behind this exacerbation was traced to hyperthermia several decades ago.[8] Despite this history, the efficacy of cooling therapy in symptomatic relief has not been firmly established in the literature. While cooling therapy does not offer disease modification, it may have promise as a safe method of alleviating symptoms and encouraging health-promoting behaviors such as aerobic exercise. Additionally, its implementation would underscore the value of the patient's subjective experience of their disease.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not cooling therapy improves functional mobility in heat-sensitive adults diagnosed with MS.

METHODS

Three randomized controlled trials were used in this review. Adults with heat-sensitive multiple sclerosis comprise the population in the studies used. The experimental intervention in each study was a form of cooling therapy, although each used a different device to achieve cooling. One study used bilateral thigh-cuffs that used fluid evaporation to remove body heat.[9] Another employed an elastic wrist sleeve with a vacuum pump to create a negative (subatmospheric) pressure gradient inside the chamber.[10] In the third study, a specialized hood used circulating fluid to conduct heat away from the participant's head and neck.[11] This intervention was compared to a control, consisting of either an absence of cooling or sham cooling (in which the participants were fitted with a device they were told was removing body heat). The outcome for all participants was one or more objective measurements of functional capability.

All articles reviewed herein were published in the English language and in peer-reviewed journals. A PubMed search was performed using the keywords cooling and multiple sclerosis. Articles were selected based on relevance to the aforementioned objective and on whether the measured outcome was patient-oriented rather than disease-oriented. The inclusion criteria consisted of RCTs published no earlier than 1999. Studies in the chosen articles excluded those younger than 18 years of age, those with relevant concomitant conditions (e.g. infections, pregnancy), and those with a recent MS exacerbation or relapse. Reported statistics were

p-values, paired *t*-test, and one- and two-way analysis of variance (ANOVA). Table 1 summarizes the demographics of each study.

Table 1 – Demographics & Characteristics of Included Studies

Study	Type	n	Age (yrs)	Inclusion Criteria	Exclusion Criteria	With-drawals	Interven-tions
Meyer-Heim (2007)[9]	RCT	20	48.7 (27-66)	Clinically definite MS Heat-sensitivity	EDSS >6.5 Infections/fever, relapse within 3 mos Use of steroids	0	Cooling therapy (thigh-cuff cooling garments)
Grahn (2008)[10]	RCT	12	50.8 (42-63)	Diagnosis of MS History of heat-sensitivity Regular exercise program Ambulates independently	Failure to meet inclusion criteria	2	Cooling therapy (one hand in heat extraction device)
Reynolds (2011)[11]	RCT	6	41.3 ± 7.3	Definite MS Heat-sensitivity	Use of certain medications* Participating in another clinical trial Pregnancy Another neural or muscular disease Exacerbation within the past month	0	Cooling therapy (head and neck cooling device)
*antihypertensive, vaso-active or diuretic drugs							

OUTCOMES MEASURED

Meyer-Heim, et al., in their single-blinded balanced crossover study, compared each participant's performance on a number of functional examinations with activated thigh-cuff cooling to their performance with sham (inactivated) cooling.[9] These examinations included the

MS functional composite (MSFC)(consisting of walking capacity, manual dexterity, and cognition) as well as in terms of postural control, knee spasticity (Modified Ashworth Scale), muscle strength of foot dorsal flexion, knee flexion (McMesin Pull Gauge), and grip strength (Jamar dynamometer).

In a similar study using randomized paired trials, Grahn, et al. measured their subjects' exercise duration on a standardized treadmill protocol with the stop criteria of symptom exacerbation and subjective fatigue.[10] Under this protocol, the speed and slope on the treadmill were alternately increased by consistent increments at three minute intervals. A baseline assessment (without cooling) was completed as a control, and one or more experimental trials with cooling via wrist cuff device were completed two to seven days after the previous trial.

Lastly, Reynolds, et al. conducted a double-blinded crossover study in which participants underwent a battery of tests three times under different conditions: true cooling via specialized hood, sham cooling, and no cooling; the participants were told that they would undergo two cooling trials in order to blind them to the presence of sham cooling.[11] The tests of functional mobility included in this battery were the six-minute walk test, the 25-foot walk test, and the timed up and go test.[11] The performance measurements (with parameters determined by the nature of each test) were then compared across the three conditions.

RESULTS

Three RCTs compared functional mobility with and without a cooling stimulus in heat-sensitive adults diagnosed with MS. Meyer-Heim, et al. studied 20 adults from 27 to 66 years of age (mean 48.7 years). Each participant completed paired trials, one with activated cooling and one with inactivated sham cooling as a control. The study was single-blinded; the

participants, but not the researchers, were blinded to which of the two trials was experimental. During each trial, the participants underwent a number of tests of functional mobility, the results of which are continuous data. No participants were said to be lost to follow-up. Tympanic temperature was not significantly altered between the active and sham cooling trials (Table 2). Skin temperature was ~4°C lower during the active cooling trials; the authors do not comment on the significance of this deviation. Significant improvement was noted in the 25-foot walk, nine-hole peg test (a test of manual dexterity), and the total MSFC ($p < 0.05$). According to the participants, the cooling device was without adverse effects.

Table 2 – Meyer-Heim, et al.: Treatment vs. Control Trials

Outcome measure	Active cooling	Sham control	*P* value
Tympanic temp. change (°C, SD)	– 0.092 (0.25)	– 0.047 (0.22)	0.126
MSFC (*z*-score, SD) T25FW (s mean, SD) 9HPT (s mean left/right) (median IQR) PASAT3 (no. correct mean, SD)	0.952 (0.88) 14.2 (10.8) 29.5 (9.6) 40.4 (16.5)	0.723 (1.11) 18.0 (17.3) 34.3 (17.1) 39.4 (15.9)	0.017 0.035 0.012 0.747
Postural sway, 30 s* (cm/s, SD) (mean displacement velocity) Eyes open Eyes closed	 2.24 (0.97) 3.98 (1.72)	 2.53 (1.05) 4.39 (2.15)	 0.65 0.55
Spasticity Knee (Modified Ashworth Scale) mean left/right (SD)	1.08 (1.0)	1.08 (0.9)	0.835
T25FW, Timed 25-Foot Walk; 9HPT, Nine-Hole Peg Test; PASAT3, Paced Auditory Serial Addition Test with a three-second interstimulus interval *10 s of the recording have been omitted systematically to avoid disturbance from delayed stabilization of the recording equipment after the person stepped onto the force plate			

Grahn, et al. studied 12 adults from 42 to 63 years of age (mean 50.8 years). Two subjects were lost to follow-up as they withdrew from the study due to self-reported relapse. As above, each participant completed paired trials. In this study, one trial was with cooling and the

other was without cooling; no sham cooling condition was used. Neither the participant nor the researchers were blinded to the presence or absence of cooling during each trial. During each trial, participants exercised until reaching a stop criterion (subjective fatigue or symptom exacerbation), and the duration of exercise was recorded as continuous data. With the studied intervention, exercise duration increased significantly as a group ($p < 0.003$, paired *t*-test)(Table 3) and improved for each subject. Body temperature was not measured and therefore could not be compared between the cooling and control trials. Adverse effects of cooling were not explicitly reported. However, a change in usual symptoms was reported by "several" subjects, who stated that, during cooling, their symptoms occurred in waves rather than as progressive fatigue. One participant reported a "tingling" in the legs rather than the "cloudy" feeling he typically experiences during exercise.

Table 3 – Grahn, et al.: Treadmill Speed & Slope in Treatment vs. Control Trials

Subject	Speed[a] (Km/h)	Slope[a] (%)	Number of paired trials	Exercise duration (min)		Cooling effect (ratio)
				Control	Cooling	
1	4.8	5 – 6	3	17.2	22.9	1.34
2	0.8	0	1	20.0	32.0	1.60
3	4.0	5 – 6	3	20.7	22.1	1.07
4	1.3	0	1	25.0	28.3	1.13
5	3.2 – 4.8	6	4	36.4	44.8	1.23
6	4.8	7 – 8.5	3	37.4	49.8	1.33
7	4.0	6 – 7	5	38.4	51.6	1.34
8	2.4	0	2	39.8	43.2	1.09
9	3.2	0	2	39.9	67.5	1.69
10	3.2	5.5 – 6	2	42.3	65.8	1.55

Group[b]	Mean ± Standard Deviation	31.7 ± 9.8	42.8 ± 16.4	1.35 ± 0.22

[a] Slopes and speeds of the treadmill were adjusted between sets of paired trials.
[b] $P < 0.01$, paired *t*-test

Reynolds, et al. studied six adults with a mean age of 41.3 ± 7.3 years; while all participants in this study were female, the authors report that this gender distribution was not by design. No subjects were reported as lost to follow-up. Participants completed a battery of tests under three conditions: true cooling, sham cooling, and no cooling. A physiotherapist conducted the battery of tests and was blinded to under which condition each trial was performed; the participants were also blinded to true and sham cooling. After resting for 20 minutes, participants were fitted with a cooling hood for 60 minutes, regardless of the presence of actual cooling or not. Following another rest period for 10 minutes, subjects began the tests. All data obtained were continuous. Body temperature (measured rectally) was found to be 0.37°C lower in the true cooling condition vis-à-vis sham and no cooling ($p < 0.01$). ANOVA was performed on the trials to determine statistical significance of outcomes measured (Table 4). In terms of the tests of functional mobility, a significant difference ($p = 0.036$) was found between true cooling and sham or no cooling on the six-minute walk test. Comparing true and sham cooling to the no cooling condition, there was also a significant improvement ($p = 0.004$) on the timed up and go. No significant difference was found between the trials on the 25-foot walk test. Participants did not experience any side effects to the experimental intervention.

Table 4 – Reynolds, et al.: Summary of Mean (SD) Performance Measurements & Statistical Comparisons Across the No, Sham, and True Cooling Conditions

	True Cooling	Sham Cooling	No Cooling
25-foot walk test (seconds) $F = 2.462$ & $P = 0.13$	5.80 (1.54)	5.82 (1.54)	6.10 (1.61)
Timed up and go (seconds) $F = 11.21$ & $P = 0.0036$	11.53 (4.63)†	12.03 (5.23)†	12.96 (5.34)
6-minute walk test (meters) $F = 4.731$ & $P = 0.036$	459.1 (116.5)††	437.7 (112.5)	414.3 (96.4)
† significant difference from no cooling †† significant difference from both no cooling and sham cooling			

DISCUSSION

Because cooling therapy did not elicit any adverse effects in any of the three studies included in this review, it appears to be a well-tolerated approach to managing symptoms of MS. However, long-term evaluation of its safety cannot be inferred from these studies, as all participants were evaluated and surveyed soon after the experimental intervention was completed. Additionally, the three studies used different devices to achieve a cooling effect; still more devices are commercially available, including cooling vests.[12] The safety of one device should not be understood as representing the safety of another. For example, some devices may reach significantly lower temperatures that could potentially cause some type of hypothermic injury. Finally, specific parameters (e.g. indications, contraindications) for the use of cooling therapy would ideally be developed before its widespread clinical application.

One common barrier with which patients are faced when starting a nonstandard therapy for a given condition is payment, as many patients are unable to cover their medical costs without financial assistance. The Multiple Sclerosis Association of America (MSAA) currently

offers “cooling and assistive equipment” (including cooling vests) for people diagnosed with MS who complete an online application and meet household income requirements.[12] Health insurance companies may not pay for cooling therapy, considering it experimental or not covered by certain specific coverage plans.

There are several limitations of the studies included in this review, some of which were explicitly mentioned within the respective text. Only Reynolds, et al. used a three-armed approach to evaluate differences between true cooling, sham cooling, and no cooling. In the study by Grahn, et al., failing to blind participants (as well as researchers) to their testing condition (i.e. the absence of sham cooling trials) introduces the confounding factor of a placebo effect. Meyer-Heim, et al. used a single-blinded approach in which the assessment raters were aware of the cooling condition (i.e. true or sham) of each trial, and it cannot be ruled out that this knowledge impacted the results of the study. For example, the raters could have subtly and unintentionally encouraged participants when they were known to be under the experimental condition.

Another challenge associated with blinding in this nature of research is that, in the study by Meyer-Heim, et al., the vast majority of participants (90%) were able to identify the sham cooling condition correctly. Reynolds, et al. addressed this issue by intermittently running cold fluid through the cooling hood during the sham cooling trials; this was reported as conveying a sensation of cold without actually affecting body temperature. However, they did not indicate whether participants were unable to discern sham from true cooling.

A limitation shared by all studies reviewed herein is small sample size ($n_1 = 20$, $n_2 = 12$, $n_3 = 6$). Grahn, et al. addressed this limitation through repeated trials with the same participants.

In their trial of 12 subjects (less 2 who were lost to follow-up), 88 trials were completed, with 26 data sets meeting the criteria for paired trials. As more data are gathered on cooling therapy with presumably promising results for MS, it would strengthen the body of evidence for studies to progressively enlarge their sample sizes.

This review of cooling therapy for heat-sensitive adults diagnosed with MS is inherently limited in itself. First, covering more than three studies would have been outside its established scope. Furthermore, only RCTs from a single database were included, which may not necessarily be representative of the entire current body of research. Other forms of research (e.g. case studies) were excluded due to the associated less rigorous standards and higher potential for confounding factors. Finally, while studies published prior to 1999 may have been informative, they were excluded in the interest of conducting an up-to-date evaluation.

CONCLUSION

Based on the best currently available evidence, cooling therapy appears to be effective in improving functional mobility in heat-sensitive adults with a diagnosis of MS. Future studies are needed to determine the optimum protocol (i.e. the ideal temperature, timing of cooling, etc.) and device (e.g. thigh-cuff vs. cooling hood vs. wrist sleeve) for this therapy. Alternate methods of blinding would benefit further research in order to control for placebo. To achieve this end, Grahn, et al. suggest experimental use of nerve blocks to eliminate cutaneous afferent input, following establishment of cooling therapy as effective. This intervention seems appropriate now in light of the demonstrated shortcomings of sham cooling for blinding.

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