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The Algotect Descriptor Index: An Algorithm for Quantifying Hyperalgesia in Response to a Topical Cold Stimulus

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Abstract

The presence of cold hyperalgesia may be an important prognostic indicator for persistent pain. However, a simple and inexpensive clinical testing method is needed. This report summarizes a series of studies in healthy individuals, in which a standardized menthol stimulus was developed alongside a sensory response tool. The menthol development studies demonstrated that increased cold pain sensitivity was associated with a change in the quality of the perceived sensation as well as increased intensity. A new scoring system, the Algotect Descriptor Index (ADI) was therefore developed that combined both intensity and quality response sub-scores. Visual analogue scale (VAS) scores for intensity of cold, heat, unpleasantness and pain were weighted according to their association with a more noxious response to cold. A list of descriptors was also weighted according to frequency of selection by cold hyperalgesic individuals and a Mean Word Score (MWS) calculated as the average value for words selected. The ADI was calculated as the sum of the VAS and MWS sub-scores (max 9). The ADI score was then assessed for its validity and reliability in two additional studies. The ADI showed a strong ability to discriminate between three sustained cold temperatures ranging from noxious (10˚C), mildly unpleasant (15˚C) to normally pleasant (20˚C). Receiver operating characteristic curve analysis also showed that ADI was a good predictor of cold hyperalgesia, showing sensitivity of 0.90 and specificity of 0.74 at a cut-off of 4.5. Test-retest reliability for ADI with a 20% menthol stimulus was also high: ICC 0.945 (95% CI 0.878-0.975). This series of studies found that a simple, inexpensive, topical cold test can discriminate between individuals with and without cold hyperalgesia. The index has shown both construct validity and test-retest reliability in healthy populations.

Keywords: Cold hyperalgesia assessment, the Algotect Descriptor Index (ADI), Visual analogue scale (VAS)

Background

The presence of cold hyperalgesia may indicate widespread pain sensitivity or central pain augmentation [1,2]. Its presence has been associated with poor outcomes in a range of chronic pain conditions [3,4] and may offer an important prognostic indicator for persistent pain. Cold pain threshold (CPT) is considered the "gold standard" method for identifying cold hyperalgesia, despite some concerns regarding its reliability and clinical applicability. Most commonly, CPT is assessed using a Peltier thermode [5]. This delivers a steadily reducing cold stimulus, and the individual indicates when the cold sensation becomes painful. There is currently no consensus about the exact temperature cut-off for designating hyperalgesia. CPT relies on a single temperature value and so does not reflect the intensity of response or the change in sensation quality (dysesthesia/paradoxical sensations) that is associated with a cold hyperalgesic response [6]. The equipment required is also relatively expensive. Content validity and clinical applicability could be improved by developing a relatively inexpensive sustained cold stimulus alongside a measurement tool that integrates sensory information and comprehensively evaluates the sensory response to the cold stimulus. This report summarises a series of 4 studies that developed a standardised menthol stimulus and evaluated the discriminative ability and reliability of a comprehensive sensory evaluation measure, in order to provide a relatively simple and inexpensive way to evaluate cold hyperalgesia in the clinical setting.

Development of a sustained cold stimulus

We have previously described the development of a topical menthol-cold stimulus that is able to discriminate between individuals with and without cold hyperalgesia. Menthol activates TRPM8 cold receptors in the skin, evoking action potentials *in vitro* in Aδ thermo-fibers and behavioral responses in animals similar to that produced by cold stimulation [7]. A small number of human studies have also demonstrated that menthol elicits a consistent concentration-dependent cold response as well as eliciting other sensations [8]. This finding has been supported by our own research [9]. This therefore suggests that normal and abnormal responses to cold could potentially be identified using a topical menthol stimulus of known concentration. In contrast to conventional CPT testing, where an individual selects from a range of temperature values, application of a single cold stimulus requires an alternative response measurement method. A number of psychophysical studies have reported that the response to cold temperature may be described as dysaesthetic (tingling, stinging or prickling) or as a paradoxical hot or burning sensation [10]. Increased cold pain sensitivity therefore seems to be associated with a change in the quality of the perceived sensation as well as a change in the intensity of sensation. It is therefore important that any sensory evaluation method incorporates both sensory quality and intensity measures.

Evaluation of different menthol concentrations: The menthol cold stimulus was developed through two iterative studies, both involving pain-free healthy adult volunteers: 32 in study 1 and 27 in study 2 [9]. A range of menthol concentrations were tested: in study 1, three concentrations in a liquid formulation plus a solvent-only control were assessed, alongside conventional CPT assessment with a Somedic Peltier thermode and standard method of limits; in study 2, the two most discriminating concentrations were formulated as gels. In each study, each participant experienced a different concentration of menthol on a separate test day. Each concentration was applied topically to a standardized contact area of the forearm and occluded. At one-minute intervals during the 15-minute menthol application period participants were asked to rate the intensity and quality of the sensation they were experiencing. Intensity of cold, heat (for study 2 only), unpleasantness and pain were recorded on a 10 cm visual analogue scale (VAS). Quality of sensation was measured every two minutes by selection of words from the McGill Pain Questionnaire (MPQ) descriptor list. These word choices were quantified using two standard MPQ indices, the Pain Rating Scale (PRS) (sum of MPQ ranking values for each different word selected) and the Number of Words Chosen (NWC) (total number of different words selected).

Results: Both studies showed significant concentration-dependent effects for sensation intensity. Study 1 compared 10%, 20% and 30% liquid concentrations and found significant differences between concentrations for VAS cold and unpleasantness ($p<0.001$) and VAS pain ($p=0.003$). Study 2 compared 20% and 30% gel formulations and similarly found significant intensity differences between concentrations: VAS cold, heat, unpleasantness, pain $p=0.002$ to $p=0.004$. There were also clear sensation quality differences between concentrations, indicating that menthol evokes a complex concentration-dependent sensory response. With the 10% menthol application participants predominantly selected cool or cold. In contrast, at 20% and 30% concentrations, participants tended to choose icy or freezing plus the noxious dysaesthetic words burning, stinging or prickly. Higher concentrations resulted in significantly higher PRI and NWC index values in each study (Table 1). Significant correlations were seen between CPT and ratings of cold intensity, pain and PRI / NWC values, suggesting construct validity.

Summary: These studies demonstrated that a topically-applied gel containing 20% menthol, combined with a response measurement approach that included both intensity and quality ratings, could be effective in discriminating between individuals with a normal or hyperalgesic response to cold.

	Study 1					Study 2			
	10%	20%	30%	$F_{(2,62)}$	p	10%	20%	$t_{(26)}$	p
PRI	7(3.8)	11.5(4.9)	12.9(5.2)	26.33	<0.001	6.3(4.3)	8.9(4.8)	-3.53	0.002
NWC	3.8(1.6)	5.2(1.8)	5.5(1.6)	19.62	<0.001	3.4(2.1)	4.5(2.1)	-3.00	0.006
PRI: Pain Rating Index; NWC: Number of Words Counted									

Table 1: Difference in McGill Pain Questionnaire index scores [mean (standard deviation)] between concentrations in Study 1 and Study 2.

Development of a sensory response algorithm for quantifying response to a cold stimulus

The menthol patch development study demonstrated that increased cold pain sensitivity is associated with a clear change in both the quality and intensity of the perceived sensation. However it also showed that a more refined, purpose-designed index was needed to identify a cold hyperalgesic response with greater sensitivity and specificity. For sensation quality, although the McGill PRI index is valuable, it was developed to describe spontaneous pain rather than evoked sensations, with the MPQ ranking values calculated accordingly. A word scoring index more specific to the cold stimulus experience was therefore needed. In addition, a single index that combined the weighted descriptor index score with VAS intensity ratings would allow normal/hyperalgesic cut-off values to be calculated.

We therefore developed the Algotect Descriptor Index (ADI) using sensation quality and intensity data from the menthol patch development studies [9]. VAS intensity scales were analysed and weighted based on their association with a more noxious response to cold. For example, both studies showed that a hyperalgesic response was always associated with reports of pain and unpleasantness (>0/10) and with high ratings of cold intensity. Similarly, only high ratings of heat (study 2) were associated with overall hyperalgesia. Based on the weighted values, the maximum score for VAS intensity ratings was 4. For a sensation quality index, the MPQ descriptor list was first reduced to the words most frequently selected by all participants during studies 1 and 2. Individual word choice for those with a hyperalgesic response (higher CPT or high PRI score) was then analysed. This showed remarkable consistency in word choice for the hyperalgesic group compared with the remaining participants. Accordingly, weightings from 1-5 were assigned to each of the 16 words, according to frequency of selection by hyperalgesic participants, with the average weighting of all words selected calculated as the Mean Word Score (MWS). The final ADI index was determined as the sum of the VAS score and the MWS, with a maximum possible score of 9.

ADI validation study: The validity of this new ADI scoring system was first evaluated using a cross-sectional study to compare the sensory response to three sustained cold temperature stimuli in a cohort of 29 healthy, pain-free participants. The ability of the ADI to discriminate between a normally noxious (10˚C), normally mildly unpleasant (15˚C) and normally non-noxious (20˚C) temperature was assessed. Criterion validity was also assessed by comparing ADI with McGill PRI scores for each cold stimulus. Following initial CPT assessment, cold stimuli were applied to the volar forearm for five minutes each, in randomised order, using a Medoc TSA II thermode. During application, participants were asked to complete VAS ratings for intensity of cold, heat, unpleasantness and pain every 30 seconds and to select descriptive words from the MPQ descriptor list every minute. ADI and PRI were calculated and participants were divided post-hoc according to CPT <>15˚C as a proxy for cold hyperalgesia.

Results: Repeated Measures ANOVA analysis showed a significant difference in ADI scores between temperatures, with higher ADI score at lower temperatures. Individual ADI components also showed significant temperature-dependent differences (Table 1). There were clear differences in word choice: 20˚C was described as cool or warm whereas at 10˚C participants reported icy/freezing, burning and prickling sensations. Those with CPT >15˚C exhibited significantly higher ADI scores at 10˚C (p=0.002) and 15˚C (p=0.001) but not at 20˚C (p=0.419) (Table 2).

		CPT<15˚C (n=19)	CPT>15˚C (n=10)	$t_{(28)}$	p
10˚C	ADI	4.21(0.34)	6.09(0.37)	-3.46	0.002
	MWS	2.26(0.12)	3.19(0.15)	-4.69	<0.001
15˚C	ADI	3.08(0.40)	5.39(0.46)	-3.58	0.001
	MWS	1.77(0.16)	2.69(0.25)	-3.30	0.003
20˚C	ADI	2.43(0.37)	2.97(0.57)	-0.820	0.419
	MWS	1.70(0.20)	1.97(0.23)	-0.862	0.396
ADI: Algotect Descriptor Index; MWS: Mean Word Score					

Table 2: Comparison between participants with CPT greater than or less than 15˚C for total ADI score and MWS descriptor sub-score [mean (standard deviation)] at each sustained temperature.

Finally ROC curve analysis showed that ADI was a better predictor of cold hyperalgesia (according to CPT group >15˚C) than PRI (Table 3).

Summary: The new ADI score showed a good ability to discriminate between temperatures and was more effective than the McGill PRI in identifying those with cold hyperalgesia as measured using a conventional CPT method.

ADI reliability study: The reliability of the new ADI score was assessed in a test-retest study using the 20% menthol gel. Twenty-six healthy, pain-free volunteers experienced the same 15-minute menthol gel application on the volar forearm on two test occasions, separated by at last 24 hours. The same response assessment method was used: VAS ratings were taken every minute and descriptors chosen every two minutes. Intra-Class Correlation Coefficients (ICC) were calculated to determine inter-day reliability.

Results: The total ADI score showed excellent levels of test-retest reliability. Quality and intensity sub-scores showed equally high reliability (Table 4).

Summary: The ADI and its subscales demonstrated good test-retest reliability.

	Area under curve	Cut-off	Sensitivity	Specificity
PRI	0.524	≥ 4.5	0.60	0.53
ADI	0.832	≥ 4.9	0.90	0.74

Table 3: Roc curve analyses for PRI and ADI showing sensitivity and specificity for predicting cold hyperalgesia, as defined by cold pain threshold >15˚C.

	ICC	95% CI	Mean Difference	Standard Error of Measurement
ADI total score	0.945	0.878-0.975	0.25	0.129
MWS score	0.938	0.862-0.972	0.11	0.082
VAS Cold	0.931	0.847-0.969	2.8	2.26
Heat	0.894	0.763-0.952	4.4	3.24
Unpl	0.886	0.746-0.949	5.1	3.65
Pain	0.928	0.840-0.968	2.4	1.45
ADI: Algotect Descriptor Index; VAS: Visual Analogue Scale; MWS: Mean Word Score				

Table 4: Intra-Class Correlation Coefficient (ICC) values, 95% Confidence Intervals (CI), mean difference between test days and standard error of measurement for ADI total score and MWS and VAS sub-scores.

Conclusion

This series of studies developed a simple, inexpensive, topical cold test that can discriminate between individuals with and without cold hyperalgesia and that could be used in a clinical setting. Following the initial development of a topical menthol stimulus using a gel formulation under an occlusive dressing, a new response measurement tool was developed that integrates information about both intensity and quality of sensation into a single index. This index has shown both construct validity and test-retest reliability in healthy populations. Further research is now needed to assess the applicability of the menthol stimulus and

ADI response system in populations with chronic pain to determine its prognostic value in indicating pain severity.

Author Contributions Statement

All three authors (PM, HAEB and AW) were involved throughout the series of studies in all aspects of design, implementation, data collection, analysis and final report writing.

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