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proof-of-concept

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Abstract

Background and aims: In recent years, focus on assessing descending pain modulation or conditioning pain modulation (CPM) has emerged in patients with chronic pain. This requires reliable and simple to use bed-side tools to be applied in the clinic. The aim of the present pilot study was to develop and provide proof-of-concept of a simple clinically applicable bed-side tool for assessing CPM.
Methods: A group of 26 healthy volunteers participated in the experiment. Pressure pain thresholds (PPT) were assessed as test stimuli from the lower leg before, during and 5 min after delivering the conditioning tonic painful pressure stimulation. The tonic stimulus was delivered for 2 min by a custom-made spring-loaded finger pressure device applying a fixed pressure (2.2 kg) to the index finger nail. The pain intensity provoked by the tonic stimulus was continuously recorded on a 0–10 cm Visual Analog Scale (VAS).
Results: The median tonic pain stimulus intensity was 6.7 cm (interquartile range: 4.6–8.4 cm) on the 10 cm VAS. The mean PPT increased significantly (P = 0.034) by 55 ± 126 kPa from 518 ± 173 kPa before to 573 ± 228 kPa during conditioning stimulation. When analyzing the individual CPM responses (increases in PPT), a distribution of positive and negative CPM responders was observed with 69% of the individuals classified as positive CPM responders (increased PPTs = anti-nociceptive) and the rest as negative CPM responders (no or decreased PPTs = Pro-nociceptive). This particular responder distribution explains the large variation in the averaged CPM responses observed in many CPM studies. The strongest positive CPM response was an increase of 418 kPa and the strongest negative CPM response was a decrease of 140 kPa.
Conclusions: The present newly developed conditioning pain stimulator provides a simple, applicable tool for routine CPM assessment in clinical practice. Further, reporting averaged CPM effects should be replaced by categorizing volunteers/patients into anti-nociceptive and pro-nociceptive CPM groups.
Implications: The finger pressure device provided moderate-to-high pain intensities and was useful for inducing conditioning stimuli. Therefore, the finger pressure device could be a useful bed-side method for measuring CPM in clinical settings with limited time available. Future bed-side studies involving patient populations are warranted to determine the usefulness of the method.

Keywords: bed-side test; conditioning pain modulation; pain assessment; pressure pain stimulation; quantitative sensory testing.

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Introduction

Dysfunctional regulation of the endogenous descending pain control is considered a relevant contributor to the manifestation of sensitization and enhanced pain across many chronic pain conditions [1–4].

It is well known from animal studies that deficiencies in descending nociceptive control may have an effect on the entire neuroaxis and provoke a situation of widespread hyperalgesia [5]. Likewise, it is known from animal studies that the status of the descending control is a balance between descending inhibition and descending facilitation [6] and important for maintaining neuropathic [7, 8] and inflammatory hyperexcitable stages [9, 10]. This balance between inhibition and facilitation could be a key phenomenon in the transition from acute to chronic pain [11].

In humans, we still lack methods available to probe separately the status of the descending facilitatory or inhibitory pathways, but can so far only assess the net balance. The conditioning pain modulation (CPM) methodology [12] has been developed as a human proxy for DNIC (descending noxious inhibitory control) as assessed in animals.

Several attempts have been made to establish normative data for CPM in large cohort studies [13, 14] and compare the different technological methods used for inducing and assessing CPM [15–17]. The general findings from those studies show that the CPM readouts are highly variable and a proportion of healthy volunteers have an anti-nociceptive CPM profile (i. e. increased pain response to the test stimulus during the conditioning stimulation) whereas others have a pro-nociceptive CPM profile (i. e. decreased pain response to the test stimulus during the conditioning stimulation). The substantial CPM variation has recently been addressed as a source of information and needs to be explored further [18].

Another general feature across CPM studies is the demand for advanced and expensive instrumentations requiring trained and skilled personnel. Only very recently the first attempt has been made to develop a simple CPM bed-side test kit which could be applicable in large-scale clinical settings [19]. The conditioning tonic painful pressure stimulus used in that recent study was an ear clip, but the pain intensity of the conditioning stimulus was relatively low and difficult to control. Therefore, refinements are needed. As it was previously suggested that pressure stimulating of the fingernail may be a useful painful tonic conditioning stimulus [20], a simple bed-side applicable method could be developed on this principle.

The aim of the present study was to elaborate on the development of a simple to use, clinically applicable bed-side tool for provoking conditioning pain stimulation by pressure stimulation of the fingernail.

Methods

Volunteers

In this cross-sectional study, a convenient sample of 26 healthy volunteers (13 women) participated (mean age: 24.0 ± 2.4 years). A total of 25 volunteers (96%) reported right as the dominant side. Inclusion criteria were age between 18 and 40 years and that all volunteers were healthy and pain free at the time of the study. The volunteers were asked to restrain from alcohol and medication 24 h prior to the test day. Furthermore, the volunteers were provided with written information and verbal explanation of the experiment and they signed informed consent before participating in the study. The study was approved by the local Ethics Committee (N-20170088) and was conducted according to the Declaration of Helsinki.

Experimental design

The volunteers were placed on an examination couch in a supine position. Measurement 1 was a test stimulus of pressure pain threshold (PPT) with a handheld electronic pressure algometer (Somedic, Hörby, Sweden), which was applied perpendicularly to the lower part of the iliotibial band on the dominant leg. A built-in display on the electronic algometer facilitated a constant rate of application of pressure (30 kPa/s) and a 1 cm^2 rubber tip was attached to the probe. The subjects held a push button and were informed to press the button as soon as they felt the pressure turning into pain. When the subjects pushed the button, the recording of the algometer terminated and produced an audible sound to notice the test performer that the recording had ended. The average of three PPT assessments were calculated (measured in kPa).

Following measurement 1, a tonic conditioning pressure pain stimulus was applied. A custom-made spring-loaded finger presser device was developed to apply constant pressure to the index fingernail (Figure 1). In previous studies, this has been proven as an efficient tonic painful pressure stimulation [20]. A metal rod (lever) was attached to an eccentric wheel. The eccentric circular wheel was solidly fixed to a rotating axle with its center offset from that of the axle. When the lever was pushed downwards by the attached spring, the eccentric wheel applied a fixed pressure to the fingernail placed below it. The pressure was measured by a 1 cm^2 and 1 cm high (mimicking the height of the fingernail from the base of the holder) custom-made strain gauge force transducer. The spring selected could be attached to different grooves marked on the metal rod to adjust the pressure to obtain 2.2 kg/cm^2 (215 kPa). As the tension of standard springs differ, the different grooves marked made it possible to adjust the length of the lever (attachment of the spring to the lever) to ensure a known fixed pressure. In addition, this option to vary the pressure allows the device to be used for stimulus-response studies. However, the slight variation in people's size of the index finger caused minor differences in the kPa applied, but pilot studies using the measured 215 kPa showed that consistent pain responses could be obtained across subjects. For the current experiment, the nail of the index finger contralateral to the dominant leg was used for the 2 min conditioning pressure stimulation. The subject rated the tonic pain intensity continuously throughout the 2 min on a 0–10 cm Visual Analog Scale (VAS "0 cm" represented "no pain" and "10 cm" represented "worst

pain imaginable"). The VAS was displayed electronically on a tablet using the application VAS app (Aalborg University, Aalborg, Denmark), which sampled 0.07 Hz corresponding to a sampling every 15th second. Following the 2 min of tonic conditioning pain, the application of measurement 2 was conducted while the finger presser device was still applied. Subsequent to measurement 2, the tonic conditioning pain was removed from the index fingertip. The subject relaxed for 5 min and measurement 3 was conducted as a control (Figure 2).

Conditioned pain modulation effect was quantified as an increase in PPT from measurement 1 to measurement 2. Volunteers with a positive (> 0) CPM effect were defined as "CPM responders" while even or negative (≤ 0) CPM effect corresponded to "CPM non-responders" [19].

Statistical analysis

Data were checked for normality by calculating data frequency in histograms, QQ-plots, and Shapiro–Wilk tests and were deemed normally distributed. Paired samples *t*-tests were applied for all continuous outcomes. Data are presented as mean ± standard deviation (SD) unless otherwise stated. Furthermore, the CPM effect is presented in relative values as percentages. Paired samples *t*-test for the CPM effect was applied to evaluate the statistical significance.

Conditioned pain modulation was calculated as the absolute difference in PPT between measurement 1 (without conditioning stimulus) and measurement 2 (during conditioning stimulus). An increase in PPT indicates a CPM effect.

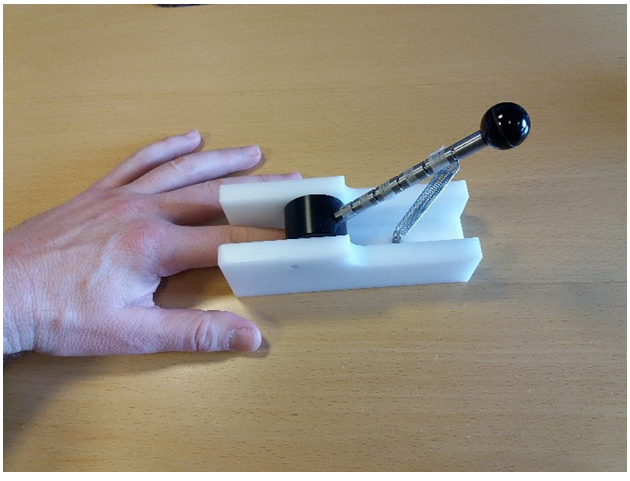

Figure 1: Illustration of the custom-made finger pressure device.

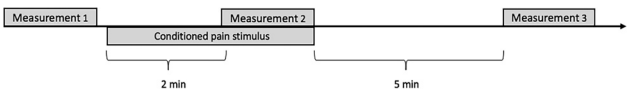

Figure 2: Timeline illustrating the timing of measurements and conditioned pain stimulus. Measurement 1, 2 and 3 represent the measurements of pain pressure threshold and conditioned pain stimulus represents the conditioned pain applied by a custom-made finger pressure device.

A significance level of 0.05 was used. All analyses were performed by means of the statistical software SPSS, Version 25.0 (SPSS Inc., Chicago, IL, USA).

Results

No adverse events, e. g. bruises or nail damage, were identified, and all volunteers completed all measurements.

PPT for measurements 1, 2, and 3 are summarized in Table 1. The CPM effect from measurement 1 to measurement 2 was 55 ± 126 kPa (mean ± SD) indicating a significant averaged CPM effect ($p = 0.034$). This equals a relative increase of PPT of 10%. The CPM responder rate showed a positive CPM effect in 18 volunteers (69%).

When CPM data were analyzed and ranked according to individual absolute data (kPa), a distribution reflecting both positive (anti-nociceptive) and negative (pro-nociceptive) CPM responders (Figure 3A) was observed. Figure 3B illustrates the relative percentage increases (anti-nociceptive) or decreases (pro-nociceptive) in the CPM effect.

Measurement 1 and measurement 3 (both without conditioning stimuli) were similar ($p = 0.268$).

The custom-made finger presser induced conditioning stimuli pain intensities, which increased steadily during the 2 min of stimulation. At 2 min, a median VAS pain intensity of 6.7 (interquartile range: 4.6–8.4) was observed (Table 2).

Discussion

This pilot-study presented a newly developed simple-to-use pressure pain stimulator to induce CPM for bed-side testing in clinical settings.

A total of 69% of the volunteers tested were defined as positive CPM responders. The study supported the concept that individual (volunteers and patients) CPM data should be sub-group analyzed based on positive (CPM responder: pain inhibition) and no/negative (CPM non-responder = pain facilitation) CPM responders. The present study represents the first attempt to conduct a proof-of-concept for bed-side studies enabling investigation of CPM in a fast and simple way.

Methodological considerations

Many different paradigms have been suggested for CPM studies [15–17, 21] which make comparisons between

Table 1: Pressure pain thresholds (PPT) and the calculated conditioned pain modulation (CPM) effect (mean ± SD). CPM effect: increase in pressure pain threshold (PPT in kPa) from measurement 1 to measurement 2 (during the tonic pain stimulation). * indicate significant differences between measurement 1 and 2 (P = 0.034).

PPT values and CPM effects				
	Measurement 1	**Measurement 2**	**Measurement 3**	**CPM effect**
PPT (kPa)	518 ± 173	573 ± 228	549 ± 230	55 ± 126*

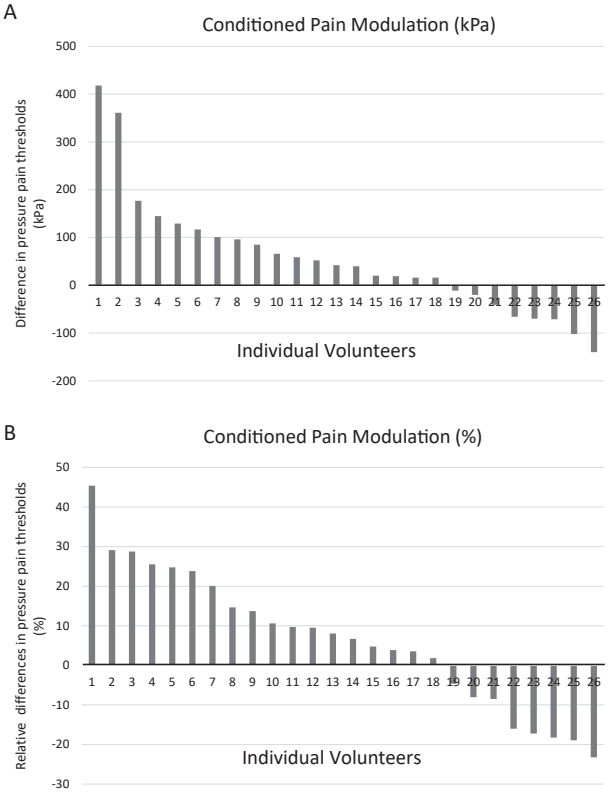

Figure 3: Frequency plot of the individual conditioned pain modulation effect for the 26 volunteers represented in absolute (A, kPa) and relative (B, %) values. Positive scores (CPM responder) indicate a conditioning pain modulation (CPM) effect as defined by an increased pressure pain threshold (PPT) during the tonic conditioning stimulation (PPT during conditioning stimulation minus PPT before conditioning stimulation).

studies difficult underlining the need of a golden standard [22]. Many attempts have been made to refine the methodology to reduce the intra-individual variation [23] without marked success. However, there is a possibility that the variation contains interesting and important information and the present study points towards a new way of analyzing CPM data.

Likewise, the reliability has been the focus of a recent CPM review [24] which clearly stated that the degree of reliability is heavily dependent on stimulation parameters and study methodology and this warrants consideration for investigators. Due to the fact that different methodologies elicit different CPM responses it has been recommended to use different methods [25] as the CPM responses may represent different processes when assessed by different paradigms.

The different CPM paradigms produce different degrees of CPM responses and the use of cold pressor pain (immersing the hand into ice water) as a conditioning stimulus and painful pressure as a test stimulus seems to be the combination eliciting the largest CPM response on average [17]. Furthermore, the response depends on the area exposed to the conditioning stimulus[26] and in some studies was found to depend on the pain intensity of the conditioning stimulus [27, 28], but this is not confirmed in other studies [29].

Despite the different CPM methodologies used and the variance experienced, attempts have been made to establish a meta-analysis for, e. g. irritable pain syndrome [30], orofacial pain [31], fibromyalgia [31, 32], psychological factors [33], aging [34] and therapeutic interventions [35].

Table 2: The conditioning (cond.) tonic painful pressure stimuli pain intensity (Visual Analog Scale in cm: VAS) during the continued 2 min finger pressure stimulation as assessed continuously on a 0–10 cm VAS (median ± interquartile range [IQR] cm).

	Cond. stimuli after 15 s	**Cond. stimuli after 30 s**	**Cond. stimuli after 45 s**	**Cond. stimuli after 60 s**	**Cond. stimuli after 75 s**	**Cond. stimuli after 90 s**	**Cond. stimuli after 105 s**	**Cond. stimuli after 120 s**
Median VAS (cm)	1.80	3.15	4.90	5.50	5.35	5.80	6.20	6.65
Percentiles VAS (cm) 25%	0.85	1.20	2.20	2.20	3.72	3.13	4.55	4.55
75%	5.08	5.78	6.80	6.93	7.85	7.95	8.48	8.40

The meta-analyses are based on averaged CPM responses, but as highlighted in previous [18, 36] and in the present studies, it is recommended to sub-group the analysis into CPM-responders and non-responders in future studies. This particular responder distribution has been shown but has not been further analyzed [13, 14]. A recent study suggesting the use of a bed-side CMP methodology [19] based on mechanical stimulation of the ear lope also showed a large intra-individual variation in the CPM effect with a CPM responder rate between 38 and 45% across repeated test sessions and thus further supports a distribution reflecting both positive and negative CPM responders. In a clinical, quantitative sensory testing profiling study on patients with painful knee osteoarthritis, a specific pain sensitization index has been developed, including the CPM response. A similar positive and negative CPM responder distribution has been found between those patients classified as sensitized and non-classified with approximately 27–38% of the OA patients being classified as sensitized and only 3% of the healthy controls [37].

Bed-side testing

The general concept is that CPM is impaired in chronic pain populations [2, 38] but with some exceptions, e. g. painful diabetic neuropathy [39] and low back pain [40, 41].

In order to apply the CPM methodology in routine screenings and in large clinical cohort studies, an easy-to-use set-up is needed. The present conditioning pain pressure stimulator is based on a simple spring-loaded actuator delivering a force of 2.2 kg to the nail of the index finger. Further, it is based on previous suggestions that this is sensitive area where tonic pain can be elicited in a reliable way [20]. For methodological studies, the conditioning pain intensity can easily be adjusted in steps by changing the position on the load shaft where the spring is attached (shorter or longer moment arm resulting in smaller or larger moment of force, see Figure 1). In the current study, the test stimulus used was the PPT as assessed by an electronic algometer. However, this device can also be replaced by a simple spring-loaded pressure actuator as previously developed [19], and pain intensity ratings can be assessed before, during, and after the conditioning stimulation using a numerical rating scale.

When comparing various CMP methodologies, it has previously been shown that the cold pressure as conditioning stimulus and the PPT as test stimulus provide the largest CPM responses in healthy volunteers [17], and the conditioning nail pressure stimulation has been shown to be at least as efficient for CPM induction as the cold pressor pain [20] which lead to the development presented in the present study. The finger pressure device induced a median pain rating of 6.7 (on a 0–10 cm VAS scale), which is considerably higher than our previous pressure-induced pain at the ear lobe (ranges from 2.2 to 4.4) [19]. This might explain the increase of CPM responders in the present study since higher conditioned pain intensities have been shown to evoke larger CPM effect [42].

It is known that within the same volunteer the CPM response can differ from session to session [17], and hence this variation is currently not fully understood but should be further explored [18].

Conclusion

The current pilot study showed that the newly developed simple-to-use finger pressure pain stimulator was efficient to induce CPM. This constitutes a proof-of-concept for a simple, clinical applicable set-up for bed-side CPM testing.

A total of 69% of the volunteers tested were defined as positive CPM responders supporting the concept that individual CPM data should be sub-grouped into positive (pain inhibition) and negative (pain facilitation) CPM responders. The bed-side method should be further investigated in clinical populations with chronic pain.

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Informed consent: Informed consent has been obtained from all individuals included in this study.
Ethical approval: The research related to human use complies with all the relevant national regulations, institutional policies and was performed in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

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