

Prospective Evaluation

Does Long-Term Opioid Therapy Reduce Pain Sensitivity of Patients with Chronic Low Back Pain? Evidence from Quantitative Sensory Testing

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Background: Long-term opioid treatment has been used extensively in treatment of chronic low back pain (CLBP) in the last decades. However, there are serious limitations to the long-term efficacy of opioids and related side effects.

Objectives: In this study we investigated whether long-term opioid treatment changes pain sensitivity of patients with CLBP.

Study Design: A prospective, nonrandomized, cross-sectional study.

Setting: Multidisciplinary pain management clinic, specialty referral center, university hospital in Germany.

Methods: Using quantitative sensory testing (QST), we compared the pain sensitivity of the low back bilaterally among 3 groups: 35 patients with CLBP undergoing a long-term opioid therapy (OP); 35 patients with CLBP administered no opioids (ON), and 28 subjects with neither pain nor opioid intake (HC).

Results: OP patients showed significantly higher bilateral thermal detection thresholds to warm stimuli on the back as compared to both ON ($P=0.009$ for left low back, $P=0.008$ for right low back) and HC subjects ($P=0.004$ for left low back, $P=0.003$ for right low back). Pain thresholds for cold and heat on the hand were similar in OP and ON groups; both showed, however, significantly reduced heat pain thresholds in comparison with HC participants ($P=0.012$ for OP, $P=0.001$ for ON). Factors such as age, sex, duration and dose of opioid intake, and self-reported pain intensity, but not depression and pain duration, correlated significantly with QST results.

Limitations: Limitations include small numbers of patients with heterogeneous opioid therapy and the nonrandomized observational nature of the study.

Conclusions: The current study demonstrated that chronic opioid intake may only reduce the temperature sensitivity but not pain sensitivity measured by QST which is a useful tool in detecting characteristic changes in pain perception of patients with chronic low back pain after long-term opioid intake.

Key words: Pain sensitivity, opioid treatment, chronic low back pain (CLBP), quantitative sensory testing (QST)

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Over the last decades, long-term use of opioids for chronic non-cancer pain has increased dramatically. However, there is limited evidence to support the efficacy of long-term opioid treatment (1). A meta-analysis of 4 studies assessing the efficacy of opioids as compared to a placebo or a non-opioid control did not show opioid-mediated pain reduction (g, -0.199 composite standardized mean difference [95% CI, -0.49 to 0.11]; $P = 0.136$), whereas a meta-analysis of 5 studies directly comparing the efficacy of different opioids demonstrated a nonsignificant reduction in pain from baseline (g, -0.93 composite standardized mean difference [CI, -1.89 to -0.03]; $P = 0.055$). Moreover, no trial evaluating the efficacy of opioids was longer than 16 weeks (2).

Several animal and human studies indicated that chronic exposure to opioids not only causes physical dependency, tolerance development, and cognitive dysfunction, but also abnormal pain sensitivity (3). Animal testing demonstrated that hyperalgesia can develop after repeated (4) and continuous (5) opioid administration, and that it resolves quickly after opioid discontinuation (6). Evidence in humans showed that short-term administration of an opioid can enhance hyperalgesia, as observed during withdrawal, and pointed to a potential role of the N-methyl-D-aspartate (NMDA) receptor system in mediating such hyperalgesic response (7). Compton et al (8) confirmed the presence of hyperalgesia in 4 healthy non-opioid-dependent men using the acute opioid physical dependence (APD) model and established that pain thresholds and tolerance to the cold pressor uniformly decreased across all APD induction methods. The phenomenon of opioid-induced hyperalgesia is thought to predominantly result from central sensitization of pronociceptive pathways and is associated with a reduced nociceptive threshold (9,10). These findings provide initial support for the existence of opioid-induced hyperalgesia (OIH), which has been conceptualized as a coexisting antagonistic process to opioid-induced analgesia and proposed as an alternative explanation for the development of analgesic tolerance to opioids.

To date, however, little is known about the long-term efficacy of opioids, especially the changes in pain sensitivity of patients with chronic musculoskeletal pain who underwent long-term treatment with opiates. A preliminary study investigating patients with chronic low back pain (CLBP) indicated that one month of oral morphine therapy was associated with lower

cold pressor tolerance times (11). Another study on hyperalgesia under long-term (2.7 years) use of opioids demonstrated that heat pain threshold assayed by quantitative sensory testing (QST) was decreased in patients with chronic pain (back pain, pelvic pain, leg/knee pain, and others) (12).

The goal of the hereby presented study was to investigate the pain sensitivity in chronic low back pain patients exposed to long-term (>1.5 years) therapy with opioid analgetics. We compared the similarities and differences of pain sensitivity measured by the QST technique among 3 populations (opioid-treated CLBP patients, non-opioid-treated CLBP patients, and healthy subjects), and analyzed the correlations between QST results and several clinical parameters such as age, sex, duration and dose of opioid medication, and comorbidity. The changes of pain sensitivity after opioid withdrawal were reported in a separate paper.

METHODS

The present investigation was approved by the Local Ethics Committee of the University of Heidelberg, Germany, and funded by the research fund of the Department of Orthopedic Surgery of the University of Heidelberg, from where the study participants were recruited. The Institutional Review Board (IRB) approved the research protocol. This study was conducted with internal resources of the department, without external funding, either from industry or elsewhere.

Participants

Three groups of subjects were studied: patients with CLBP undergoing opioid therapy (group OP), those who suffered from CLBP but had not been treated with opioids for at least 3 months (group ON), and a healthy control group with neither pain nor opioid therapy (group HC). Based on our pilot study, we estimated that the inclusion of 27 subjects in each group would result in obtaining an 80% certainty of detecting a 1° celcius difference in the mean pain thresholds with a standard deviation of less than 3° celcius.

Interventions

The investigation was performed prospectively upon patients, without change in their normal course of treatment. Thus, the IRB waived the requirements for specific consent for inclusion. However, all patients were informed about the nature of the study with adherence to all confidentiality and Health Insurance Portability and Accountability Act (HIPAA) requirements.

Pre-Enrollment Evaluation

The patients had already undergone all conventional forms of biomedical treatment and had been referred to our clinic owing to the failure of standard therapy, including long-term opioid therapy. All patients were seen and examined by the head of the Pain Center at the Department of Orthopedic Surgery to decide whether they were suitable for the assigned treatment and to verify that no sensory deficits existed. Before admission, each patient filled out a questionnaire giving information on demographic data, pain location, pain intensity on a visual analogue scale (VAS: 0 representing no pain, 10, the worst pain imaginable), pain pattern, pain duration, clinical diagnosis, and medications, including opioid and non-opioid analgesics. A urine test was conducted to detect illicit drug use. The mean duration of opioid intake was 1.5 years.

Inclusion and Exclusion Criteria

The following inclusion criteria for patients were adopted:

- 1) age between 20 and 70 years;
- 2) a history of at least 12 weeks of chronic myofascial low back pain without radicular sensation before enrolment in this study (grade II and higher chronicification according to von Korff et al [13]);
- 3) opioid therapy defined as an intake of a daily morphine equivalent dose of at least 30 mg for more than 3 months (for the standardized data analysis, we used the following conversion ratios between an oral dose of morphine and other opioid analgesics: 1 mg morphine = 0.65 mg oxycodone, 0.25 mg methadone, 5 mg tilidine, 0.01 mg fentanyl, 0.13 mg hydromorphone, 5 mg tramadol);
- 4) non-opioid pain medication in the ON group was allowed;
- 5) healthy participants (control group) had no pain and took no medication in the past year.

The exclusion criteria for all groups were

- 1) sensory deficits due to diabetes, alcoholic neuropathy, severe thyroid disease, spinal stenosis, or liver or kidney diseases;
- 2) interventional pain management procedures that might alter QST responses, including neuroaxial or local anesthetic block, within the previous 3 months;
- 3) major psychiatric disorders requiring recent hospitalization, such as schizophrenia or psychosis;

- 4) infection or acute injury at the QST site;
- 5) illicit drug intake as determined by a urine test or a negative urine test for opioid-treated patients.

The inclusion criteria for the diagnosis of depression were:

- 1) recognition of a current and at least moderate depressive episode according to the International Statistical Classification of Diseases and Related Health Problems (version 10);
- 2) a minimum score of 25 on the Center for Epidemiologic Studies Depression Scale (CES-D), German version (Hautzinger, 1993 #249).

Description of Interventions

QST was performed using the Thermal Sensory Analyzer TSA II (Medoc Inc., Ramat Ishai, Israel) and was carried out in a quiet room maintained at 20 - 25° celcius every day between 10 a.m. and noon. A contact thermode (3 × 3 cm) was gently attached and secured with a band onto the nondominant hand and the low back (bilaterally) of each subject. The baseline temperature was 32°C. The measured parameters were thermal detection thresholds including cold detection thresholds (CDT) and warmth detection thresholds (WDT), and thermal pain thresholds including cold pain thresholds (CPT) and heat pain thresholds (WPT).

Testing of CDT and WDT

Subjects were instructed to stop stimulation when they first perceived an increase or decrease in temperature from the baseline (32°C). The test was performed 4 times within one session in each patient.

Testing of CPT and WPT

Subjects were instructed to stop stimulation when they first perceived painful sensation, as temperature decreased (CPT) or increased (WPT) from the baseline of 32°C. The testing was performed 3 times within one session in each patient.

The temperature at which the subject stopped the stimulation was recorded as threshold temperature (°C). The cut-off temperatures were 0°C and 50°C.

Statistical Analysis

According to the Shapiro-Wilk test, the values of QST were not normally distributed. Thus, the Kruskal-Wallis test was used to analyze differences among the 3 groups, and the Mann-Whitney U-test, adjusted by

Bonferroni, between the 2 patient groups. Spearman's rho and Pearson's correlation analyses were used to examine the relationship between patients' QST values and age, sex, depression, duration of pain, duration of opioid medication, dose of opioids, and subjective pain intensity. All tests were performed with SPSS v16 software (SPSS, Chicago, IL, USA). For each statistical test, the significance level was set at $P \leq 0.05$.

RESULTS

Participant Flow

A total of 98 patients and healthy subjects were recruited for the study: 35 in group OP, 35 in group ON, and 28 in group HC (Fig. 1). One patient in group Op was excluded after recruitment as spinal stenosis was diagnosed upon MRI examination. Two patients were excluded due to invalid assay results. Table 1 shows the clinical data of all 3 groups. Overall, there were no statistically significant differences in age, sex, depression scores, pain duration, and pain intensity between the

2 patient groups (Chi-square test) ($P > 0.05$). The age and sex of subjects of all 3 groups were comparable ($P > 0.05$).

Investigation of QST Parameters

Differences in Thermal Detection Thresholds Among Groups

There were significant differences in warmth detection thresholds in the left ($P = 0.005$) and right ($P = 0.001$) low back among the 3 groups. CLBP patients administered no opioids demonstrated no differences from healthy subjects. Opioid-treated patients exhibited significantly higher bilateral thermal detection thresholds to warm stimuli on the back as compared to ON patients ($P = 0.009$ for left low back, $P = 0.008$ for right low back) as the temperature changed from the baseline (32°C). They also showed notably higher warmth detection thresholds than healthy participants ($P = 0.004$ for left low back, $P = 0.003$ for right low back) (Fig. 2).

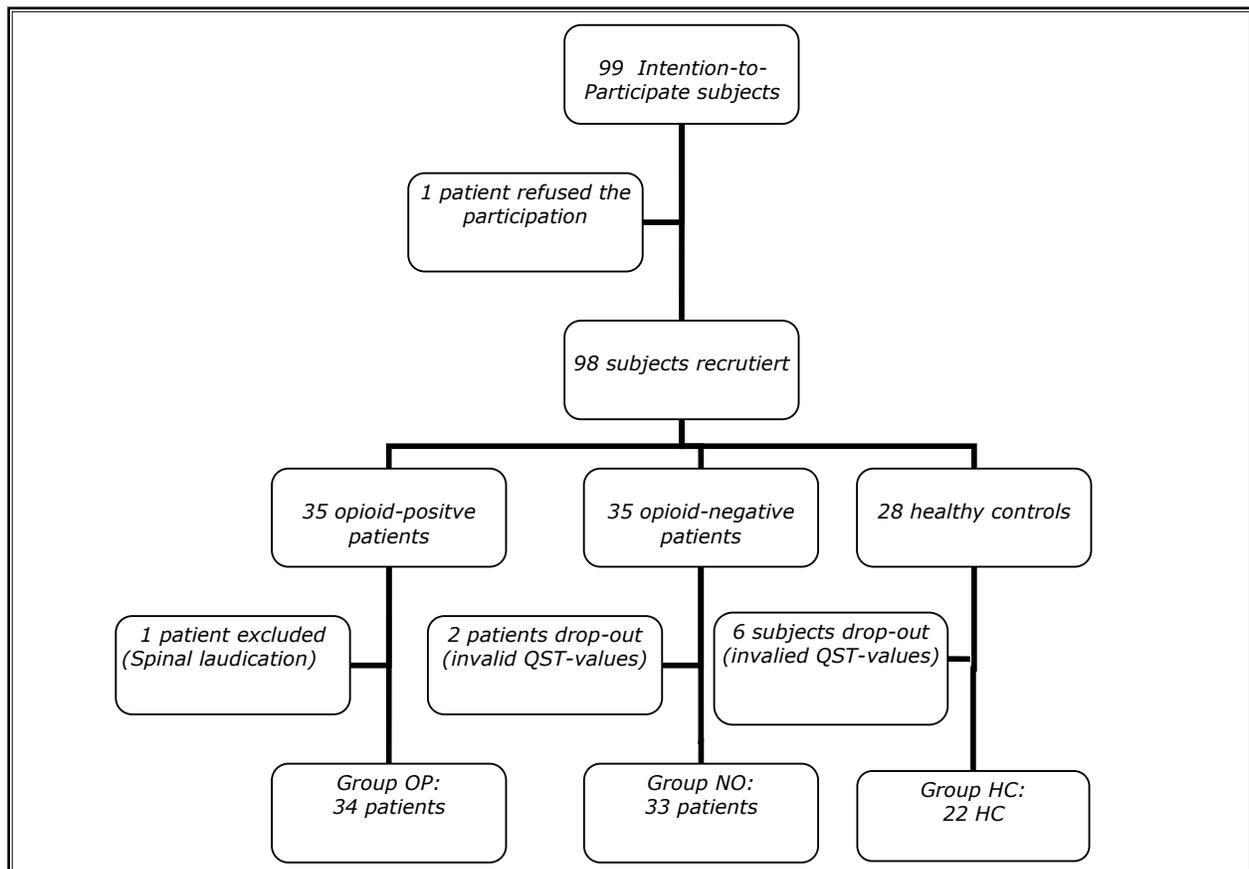


Fig. 1. Flow diagram of study participants

Table 1. Characteristics of study subjects.

	Group OP (n=34) opioid-treated patients	Group ON (n=33) nonopioid-treated patients	Group HC (n=22) healthy subjects
Age (years)	48.36 ± 12.41	46.58 ± 8.91	47.09 ± 10.28
Female	45.5 %	60.6 %	59.1 %
Male	54.5 %	39.4 %	40.9 %
Diagnosis	Chronic low back pain	Chronic low back pain	No pain
Pain history duration	10.30 ± 9.95 years	7.13 years ± 7.16	0
Pain intensity (VAS) now	6.25±1.94	5.26±2.31	0
Opioid treatment history duration	16.61 ± 19.11 months	0	0
Daily dose, morphine equivalent dose	124.09 mg/d ± 111.58	0	0
Depression (CES-D)	47.6 %	44.4 %	0%
Adjuvant	NSAIDs (2%) antidepressants (1%)	NSAIDs (5%) antidepressants (6%)	0

CES-D: Center for Epidemiologic Studies Depression Scale, German version.

NSAIDs: Non Steroid-Anti-Inflammatory-Drugs.

VAS: Visual Analogue Scale.

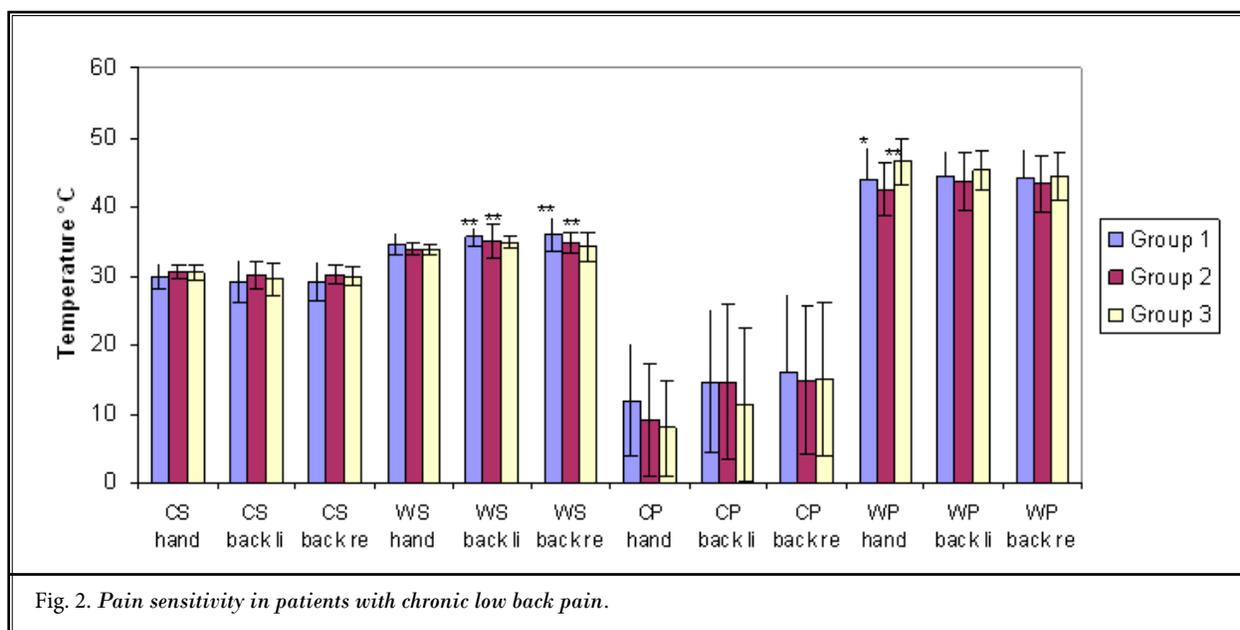


Fig. 2. Pain sensitivity in patients with chronic low back pain.

Pain Detection Thresholds Among Groups

There were significant differences in heat pain thresholds on the palmar surface of the hand among the 3 groups ($P = 0.012$) (Fig. 2). Both patient groups showed considerably reduced heat pain thresholds as compared to the healthy control group ($P = 0.012$ for OP patients, $P = 0.001$ for ON patients). No evident discrepancies of cold or heat pain thresholds were found among the patient groups.

Correlation Between QST Results and Clinical Parameters

Seven clinical parameters -- age, sex, duration of pain, duration of opioid medication, dose of opioid medication, comorbidity (e.g. depression), and subjective pain intensity -- were analysed in relation to QST results. All these factors, except for duration of opioid medication and comorbidity, correlated with the QST results (Table 2).

Table 2. Spearman's-Rho (R) correlation between QST responses of low back and clinical factors.

	CDT	WDT	CPT	WPT
Age	-	-	-	back left, R=-.231* back right R=-.239*
Sex	-	hand, R=.337***	-	back left, R=.238* back right, R=.232*
Pain sensitivity (VAS)	back left, R=-.364** back right, R=-.344**	back left, R=.274* back right, R=.364**	-	-
Dose of opioid intake	back right, R=.453**	-	-	-
Duration of opioid intake	back right, R=.269*	-	-	-

CDT: Cold Detection Threshold.

WDT: Warmth Detection Threshold.

CPT: Cold Pain Threshold.

WPT: Warm Pain Threshold.

VAS: Visual Analogue Scale.

Age

The older the subjects were (both patients and healthy participants), the lower was their threshold for heat pain (WPT) on both sides of the low back (right: $P = 0.031$, $R = -0.231$; left: $P = 0.020$, $R = -0.239$).

Sex

Male patients showed higher detection thresholds for warmth in the hand (WDT: $P = 0.001$, $R = 0.337$) and higher pain thresholds for heat in the left ($P = 0.026$, $R = 0.238$) and right low back ($P = 0.030$, $R = 0.232$) than women.

Pain sensitivity

The pain intensity subjectively recorded by patients correlated with the cold detection thresholds of the left ($P = 0.003$, $R = -0.364$) and right low back ($P = 0.005$, $R = -0.344$), and warmth detection thresholds of the left ($P = 0.026$, $R = 0.274$) and right low back ($P = 0.003$, $R = 0.364$), but not with the pain thresholds of cold or heat.

Opioid dosage

Cold detection threshold on the right low back correlated with the daily dose of opioids ($P = 0.008$, $R = 0.453$).

Opioid duration

Cold detection threshold on the right low back correlated with the duration of opioid intake ($P = 0.033$, $R = 0.269$); the longer the opioid duration, the quicker the response to cold stimuli.

DISCUSSION

The present study demonstrated that long-term opioid treatment significantly increased thermal detection thresholds, but not pain thresholds, in patients with chronic low back pain. Moreover, the perceived temperature thresholds, and not the pain thresholds, correlated with pain intensity. In brief, long-term opioid therapy in our patients did not bring about the presumed result of increased pain thresholds, but a side effect of altered sensory perception.

Quantifying Pain

QST of thermal perception is a standardized computer-controlled method and the only technique that enables measurement of the small fibers of the nervous system (C and A- δ fibers, unique for the sensation of pain transmission). In other words, QST is the sole clinical procedure that quantitatively assesses the function of somatic small nerve fibers – from the peripheral receptors to the central nervous system (14,15).

In this study, a battery of 4 thermal QST parameters was used: cold and warmth detection thresholds, as well as thresholds for cold pain and heat pain. We tested both healthy subjects and non-opioid-treated patients and used their baseline QST responses to ensure the differentiation of QST results due to opioid usage or pre-existing low back pain. The palm of the hand was additionally chosen as a control region to enable detection of any opioid-induced hyperalgesia independent of pre-existing low back pain (3). Both of the persons performing the tests were female, excluding sex of

the test personnel as a confounding factor (16,17). To rule out any influence of fluctuations in ambient temperature on QST results, the temperature of the test room was kept stable at 20 - 25°C (18,19).

No Evidence of Analgesic Efficacy of Long-Term Opioid Therapy as Assessed by QST

In this study, the only discrepancy between the patients of groups OP and ON was opioid intake.

Overall, there were no statistically significant differences in age, sex, depression scores, pain duration, and pain intensity between the 2 patient groups. Therefore, the finding that opioid-treated patients had higher detection thresholds to thermal stimuli may indicate that opioid medication solely induced the changes in thermal perception. This result is concordant with findings in cats, indicating that warmth detection threshold was increased after opioid exposure (20).

The mechanisms of delayed thermal responses due to opioid intake may be as follows:

Firstly, cold sensation is transmitted by myelinated A- δ fibers and warmth, by unmyelinated C fibers. Numerous studies confirmed that opioids selectively inhibit the activity of the posterior horn of the spinal cord and thereby affect the conductivity of afferent C fibers (21-23). It was demonstrated in animal models that the transmission of information via A- δ fibers can be eliminated only by morphine at very high doses (from 2 mg/kg), which are rarely prescribed for pain therapy (23). On this supposition, our results established that long-term opioid use (>16 months) may inhibit afferent C fibers in the periphery and thus increase the thermal detection threshold.

Secondly, opioids can additionally cause sedation, reduced vigilance, and lowered concentration in patients with chronic pain (24,25). The delayed QST responses to thermal stimuli might therefore be an expression of a reduced reaction time due to opioid use.

Correlations Between Clinical Factors and QST Values

We found significant correlations between QST responses and age, sex, opioid intake duration, opioid dose, and subjective pain intensity.

Older patients were more sensitive to heat stimuli in our study. It may be explained by the fact that older patients were more sensitized peripherally due to longer history of low back pain. This finding, however, is in contrast to other studies (26-28).

In agreement with existing literature, female patients and healthy subjects showed significantly lower thermal detection thresholds (29,30) and pain thresholds (18,26) than male patients. This may be attributable to differences in sensory processing between men and women (17,31) or to hormonal influences (32).

The longer the duration of pain, the quicker were the patients' reactions to cold stimuli. This correlation confirms the assumption that chronic pain may cause pain sensitization (33-35) and, therefore, the pain duration correlates with the magnitude of sensitization. Yarnitsky and Ochoa (36) reported lowered pain thresholds after selective blockade of A- δ fibers. Furthermore, they found that painless cold stimuli lost their cold character after blocking the said nerve extensions. Instead, subjects reported a burning sensation. The information of cold sensation is conducted by A- δ fibers and their activity blocks the function of C fibers. Therefore, blocking A- δ axons leads to disinhibition of C fiber activity and increases pain sensitivity. Strigo et al (37) found that cold outdoor temperatures increased thermal pain thresholds by stimulating A- δ fiber activity and inhibiting that of C axons. Moreover, peripheral application of cold stimuli lowers simultaneously recorded laser-evoked potentials (38).

In contrast to these phenomena, inhibition of C fiber activity by opioids might boost the functioning of A- δ nerve extensions. The higher the dose of opioid intake, the stronger the block of C fibers may become, the less the activity of A- δ fibers may be hindered, and the quicker may the response to cold stimuli may be generated. To our knowledge, we are the first to describe this phenomenon; further investigations should be performed to confirm our findings.

Limitations

A significant limitation of this study was our inability to assay the thresholds of interest prior to initiating opioid intake and to grade the drug dosage as demonstrated by Hooten et al (39). Although we found no differences in pain thresholds between the 2 CLBP patient groups, this may not necessarily indicate lack of opioid-induced hyperalgesia. Thus, we cannot rule out the possibility that the long-term opioid therapy patients became more pain sensitive over time since the beginning of treatment. We realize that the current investigation was a cross-sectional comparison, and that a causal inference can only be derived from a prospective study, which should be performed in the future.

Another limitation was the heterogeneity of the Op patient group regarding doses, forms, and duration of opioid intake. Due to a small number of patients, we were not able to define alternative groups according to the aforementioned parameters. These points should be considered in further studies.

CONCLUSION

The current study clearly demonstrated that QST is a useful tool in detecting characteristic changes in pain perception of patients with CLBP after long-term opioid intake.

Our findings provide further insight into the long-term efficacy of opioid therapy and suggest that a disproportionate increase of opioid dose may reduce the thermal thresholds and, therefore, the pain perception of patients.

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