Quantitative Evaluation of Pain with Pain Index Extracted from Electroencephalogram

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**Abstract**

**Background:** The current pain assessment methods are strongly subjective and easily affected by outside influences, and there is an urgent need to develop a reliable objective and quantitative pain-monitoring indicator. The aim of this study was to evaluate the feasibility of using Pain index (Pi) to assess pain symptoms in pain patients.

**Methods:** Subjects were enrolled from patients seeking treatment at Pain Medicine Center of China Medical University Aviation General Hospital from October 2015 to December 2016, such as postherpetic neuralgia, spinal cord injury, femoral head necrosis, lumbar disc herniation, trigeminal neuralgia, complex regional pain syndrome, perineal pain, phantom limb pain, etc., (pain group, \(n = 111\)), as well as healthy volunteers without subjective pain (control group, \(n = 100\)). The subjective pain symptoms in pain patients were evaluated by Pi and visual analogue scale/numerical rating scales (VAS/NRS), respectively, and the relationship between them was analyzed using single factor correlation analysis and multiple factor regression analysis.

**Results:** Pi levels in the pain group were significantly higher than those of the control group (\(t = 6.273, P < 0.001\)), the correlation analysis of Pi and VAS/NRS score in the pain group showed that the Pearson correlation coefficient was 0.797 (\(P < 0.001\)); After adjusted for types of pain, pain sites, medication, gender, and age, Pi was found to be independently correlated to VAS/NRS score (\(P < 0.001\)).

**Conclusions:** Pi significantly correlates with VAS/NRS score, might be used to evaluate the subjective pain symptoms in patients and has good research and application value as an objective pain assessment tool.

**Key words:** Electroencephalogram; Pain; Wavelet Algorithm

**Introduction**

Pain is an unpleasant subjective feeling, an emotional experience as well as a protective or pathological response associated with tissue damage or potential tissue damage. Pain has been recognized as the fifth most important vital sign following respiration, pulse, body temperature, and blood pressure by The International Association for the Study of Pain.\(^{[3]}\) In the pursuit of high quality of life in today’s society, clinicians must heed the increasing demand for standardizing pain treatment, and the first condition of standardizing pain treatment is to develop an objective quantitative assessment of pain.\(^{[2]}\)

At present, subjective scales such as visual analog scale (VAS), numerical rating scales (NRS), and verbal rating scales (VRS) are widely used in clinical practice. Heart rate or blood pressure variability, the electrical conductivity of the skin and other physiological parameters are also used to assess the degree of pain in patients. However, the assessment methods mentioned above are strongly subjective and easily affected by outside influences; therefore, there is an urgent need to develop a reliable objective and quantitative pain-monitoring indicator.\(^{[3,4]}\) In recent years, a series of studies have found that electroencephalogram (EEG) as a noninvasive, safe, and reliable means of examination, can be used in the field of pain assessment. Multiple studies confirm
that pain can cause significant changes in EEG signals in multiple brain regions and in multiple frequencies. EEG monitoring is thus expected to be an effective and objective indicator for assessing pain.\(^{[4-7]}\)

Pain index (Pi) is a pain recognition indicator based on brain wave, or EEG, signals. The pain-related data in the whole frequency band of the brain waves are then transformed by wavelet algorithm to obtain the Pi value (range 0–100), to objectively reflect the existence and severity of subject’s pain symptoms. The aim of this study was to evaluate the symptoms of pain in subjects with VAS/NRS score commonly used in clinical work and Pi value; by analyzing the correlation between the Pi index and the traditional VAS/NRS, the current work is a extremely rare study to explore the feasibility of Pi index as an objective quantitative measure of EEG indicator and the practicability of guiding clinical practice.

**METHODS**

**Ethical approval**

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of China Medical University Aviation General Hospital (No. HKZYY20160506). Informed written consent was obtained from all patients and healthy volunteers before their enrollment in this study.

**Subjects**

Subjects were enrolled from patients seeking treatment for pain at Pain Medicine Center of China Medical University Aviation General Hospital from October 2015 to October 2016, including postherpetic neuralgia, spinal cord injury, femoral head necrosis, lumbar disc herniation, trigeminal neuralgia, complex regional pain syndrome, perineal pain, phantom limb pain, etc., (pain group, \(n = 111\)), and healthy volunteers without subjective pain (control group, \(n = 100\)) were also enrolled. Both Pi and VAS/NRS were used to assess the subjective pain symptoms of the subjects.

Inclusion criteria: (1) age 18–85 years; (2) pain patients: pain related to postherpetic neuralgia, spinal cord injury, femoral head necrosis, lumbar disc herniation, trigeminal neuralgia, complex regional pain syndrome, etc.; (3) healthy volunteers: body mass index 18–25 kg/m\(^2\); vital signs axillary temperature 36.1°C–37.0°C, heart rate 60–100 beats/min, respiration rate 12–24 respirations/min; systolic blood pressure (90–140 mmHg, 1 mmHg = 0.133 kPa), diastolic blood pressure (60–90 mmHg); corrected visual acuity >0.8; normal activity tolerance (the subjects can climb 4 stairs); (4) voluntary acceptance of this trial and signing the informed consent.

Exclusion criteria: (1) central nervous system diseases, such as epilepsy, cerebral infarction, or cerebral hemorrhage history; (2) mental disorders; (3) long history of taking psychotropic drugs.

**Electroencephalogram measurement method**

Subjects’ forehead and the mastoid behind the ears were cleaned, and the EEG electrodes of the multifunction combination monitor HXD-I (Heilongjiang Huaxiang Technology Co., Ltd., Heilongjiang, China) were placed on subjects’ forehead, 2 cm above the midpoint between the eyebrows [FZ, Figure 1] and above the bilateral eyebrows [left FP1, right FP2, Figure 1]; the reference electrodes were placed on the bilateral earlobe [left A1, right A2, Figure 1]. After the subject rests for 2 min, EEG monitoring begins, which will record EEG data continuously for 40 min. All subjects were asked to try to remain silent and to stay still during the test procedure.

**Pain index calculation**

Using EEG analysis software package (Beijing Easymonitor Technology Co., Ltd., Beijing, China) based on the wavelet algorithm, which has been previously used for analyzing brain waves,\(^{[8]}\) the repeatable and regular changes when pain present was extracted from brain waves as the characteristic indicator of subjective pain. Two channels of EEG data were recorded by HXD-I and were then implemented to reduce the complexity of the features through continuous and discrete wavelet transform. The continuous wavelet transforms, binary discrete wavelet transform and frequency domain reconstruction algorithm in wavelet analysis were first introduced to deal with the specific EEG data vector. For the collected EEG signals, under the sampling frequency, sampling accuracy, and time window, the vector set of each waveform signal is generated by discrete processing:

\[ f_i (x) = [x_1 x_2 x_3 \ldots x_{m-2} x_{m-1} x_m] \]

\(i: \) the number of EEG leads, \(m: \) the number of vector elements.

Each lead EEG data acquisition window is S seconds, composed of each lead of EEG data vector Ni. Preprocessing of vector data for removal of DC components:

\[ f (x) = f (x) – Av; \]

\(Av: \) Direct circuit component of a vector.

![Figure 1: Examination of electroencephalogram.](image)
For the preprocessed brain wave data, waveform recognition algorithm, spectral analysis algorithm, and wavelet analysis algorithm are applied. Wavelet analysis algorithm, as the latest mathematical tool for brain wave computation, has significant computational advantages. Wavelet algorithm definition:

If \( f(x) \) function is the signal for space domain \( \{ -\infty, +\infty \} \), continuous wavelet transform algorithm formula is as follows:

\[
W_c f (\tau, a) = \frac{1}{\sqrt{a}} \int f(x) \phi \left( \frac{x - \tau}{a} \right) dx
\]

For the calculation formula of wavelet frequency domain, the following expressions are used:

\[
WT_x (a, \tau) = \frac{1}{\sqrt{2\pi}} \int X(\omega) \psi(\omega) e^{-i\omega t} d\omega
\]

The spectral analysis algorithm uses the discrete Fourier formula:

\[
F(\omega) = f(t) = \int f(t) e^{-i\omega t} dt
\]

The inverse transformation uses the following formula:

\[
f(t) = \hat{F}(\omega) = \frac{1}{2\pi} \int F(\omega) e^{i\omega t} d\omega
\]

For brain wave data, first apply binary conversion algorithm and waveform reconstruction algorithm in wavelet analysis to process specific brain wave vector data, select specific wavelet generating function, construct an n scale, from \( 2^0 \) to \( 2^n \) to conduct binary conversion algorithm:

\[
(Wf(2^n), x) \quad j \in \mathbb{Z}
\]

A set of wavelets transform basis functions for bandpass filter banks can be obtained:

\[
(Wf(2^n), x), (Wf(2^{n-1}), x), (Wf(2^{n-2}), x)
\]

The power WLE (I) of the waveform potential of each wavelet base reconstruction function can be obtained

For each guided brainwave vector:

\[
f(x) = [x_1, x_2, x_3, \ldots, x_{n-2}, x_{n-1}, x_n]
\]

The power spectrum function is calculated synchronously, and the formula is calculated by using fast Fourier transform:

\[
X(\omega) = \int f(x) e^{-i\omega t} dt
\]

The calculation window is n, which can obtain the alpha wave component of 8–13 Hz, the component of delta wave of 0.5–4 Hz, the theta component of 4–8 Hz, and the beta wave component of 13–30 Hz, as well as the dominant frequency, edge frequency, and central frequency, and the initial phase pH (Hz) of each frequency component.

The generating function was defined as the first derivative of the smoothing function (spline function), and 64 points were constructed, scaling from \( 2^0 \) to \( 2^n \) through the dyadic wavelet transform.

The weighted items of each sub-index extracted from EEG (i-series metadata) were acquired through decomposing of different EEG data vectors on transformation characteristic weighting sequence by using multi-layer calculation and multiple regression iteration method. \( Pi \) was calculated by combining the weighted items of each sub-index \( (a_1, a_2, \ldots, a_n) \) as the multiple regression weighting coefficients.

\[
Pi = (a_1, a_2, \ldots, a_n) \quad & (i_{10}, i_{15}, i_{23}, i_{35}, i_{45}, i_{48}, i_{66}, i_{70}, i_{77}, \ldots)
\]

**Pain assessment**

Pain patients and healthy volunteers were required to wear multi-functional combination monitor HXD-I EEG acquisition electrodes, and the monitor display was placed against subjects’ back. Subjects were asked to breathe calmly, and after 2 min, investigator A identified the intensity of the pain stimuli on the VAS/NRS scale. VAS/NRS data were recorded by investigator B, and investigator C recorded the Pi value on the monitor every 5 min. The 8 continuous VAS/NRS scores and the Pi values of the same subject in 40 min were then averaged to obtain an average value. Complete data entry was recorded by two data entry personnel according to subjects’ numbering order, and then third data entry personnel conducted to review and comparison by validity test. For any inconsistent data recorded by the two data entry personnel, reviewing of raw data were conducted, until data in both databases exactly the same, to avoid man-made error in the data entry process.

**Statistical analysis**

Quantitative data were presented as the mean ± standard deviation (SD) for normally distributed continuous variables, or as the median for nonnormally distributed continuous variables. For continuous variables, Student's \( t \)-test or the Mann-Whitney \( U \)-test was used, as appropriate, for group-wise comparisons. All tests were two-sided. The Pearson correlation analysis was used to analyze the correlation between variables. A significance level of \( P < 0.05 \) was considered statistically significant. SPSS 13.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. The above data analysis was conducted and completed by two data analysts independently.

**Results**

**Clinical characteristics of study population**

A total of 211 patient samples (101 males and 110 females, ages 18–85 years) were successfully obtained in this study by using a multifunctional combination monitor (HXD-I). A total of 100 healthy volunteers (54 ± 14 years) and 111 pain patients (60 ± 16 years) were enrolled in this study. Among the pain patients, the Pain Group includes 52 cases related
to postherpetic neuralgia, 16 cases related to neuropathic pain after spinal cord injury, ten cases related to trigeminal neuralgia, eight cases related to femoral head necrosis, six cases related to perineal pain, five cases related to lumbar disc herniation, four cases related to tumor, four cases related to complex regional pain syndrome, two cases related to phantom limb pain, and three cases related to other causes of pain. As for the pain sites, the pain group includes 33 cases on the lower limb, 27 cases on the abdomen and back, 19 cases on the abdomen, nine cases on the upper limb, nine cases on the dental periphery, seven cases on the head, four cases on the waist, and three cases on the perineum. Significant differences were observed in the distribution of Pi between healthy volunteers and patients with pain.

Pi value calculated from quantitative EEG in the pain group (pain group, n = 111) was significantly higher than that in healthy volunteers without pain symptoms [control group, n = 100, 5.5 ± 0.3 vs. 10.9 ± 0.4, t = 6.273, P < 0.001].

**Pain index and the visual analogue scale/numerical rating scales score were significantly correlated**

The correlation analysis between Pi value and the subjective VAS/NRS score in pain patients showed the Pearson correlation coefficient was 0.797 [P < 0.001, Figure 2], suggesting that the two values had a good correlation.

**Multivariate stepwise linear regression analysis of pain index influencing factors**

Further analysis of the influencing factors on VAS/NRS score using the multivariate stepwise linear regression revealed variables such as the type of pain, pain site, medication, age, and sex did not enter into the final equation. Only Pi score entered into the multivariate stepwise linear regression equation. Pi and VAS/NRS score were independently correlated [P < 0.001, Table 1].

**Discussion**

Pain is a subjective negative feeling of the human body, with strong individual differences. Because feelings and clinical manifestations of pain vary among individuals, how to objectively and reliably assess pain is the first problem clinicians face in treating pain symptoms. Pain is widely seen in the course of various diseases, or acute traumatic pain caused by surgery, rheumatoid arthritis, late-stage cancer pain and other chronic pain, as well as pain caused by herpes zoster, spinal cord injury. Pain is one of the most common clinical complaints. Effective pain assessment method can not only prove the true existence of patients’ subjective feeling of pain but also quantitatively analyze the degree of pain and analgesic demand, as well as evaluate the clinical efficacy of analgesic drugs. Such a method is extremely important in guiding clinical practice and scientific research. At present, the pain assessment tools widely used in clinical practice are VAS, VRS, NRS, and Wong-Baker Faces Pain Intensity Scale and other subjective assessment scales. However, these subjective scales are vulnerable to subjective influences, evaluation lag and other influencing factors. Yu et al.,[3] relying on a number of objective physiological indicators, have developed heart rate variability, blood pressure variability, analgesia nociception index, skin electrical conductivity and other possible monitoring indicators for pain. However, these pain-monitoring indicators have great volatility and are vulnerable to being affected by many factors. Although the modulation of the pain-sensory nerve conduction pathways is complex, in theory, EEG can directly analyze neuronal activation, evaluate the EEG components of pain activity, and provide an advanced method for processing complex pain information.[1] Bispectral index, which is an EEG monitoring index widely used in clinical practice, can only reflect the level of consciousness in the cerebral cortex and cannot be used as an indicator of the body’s response to nociceptive stimuli. At present, there is still lacking an advanced and reliable objective quantitative measure of pain used to guide clinical practice.[5]

In recent years, a number of studies have found that pain can cause significant and specific changes in multi-brain region and multi-frequency EEG signals. Zhen et al.,[4]...
conducted quantitative drug EEG monitoring on 15 patients undergoing orthopedic surgery under local anesthesia, and found that patients’ prefrontal two-channel α1-band power percentage reduced significantly and that it can be a good reflection of the degree of postoperative pain. Nir et al. conducted continuous EEG analysis on 18 healthy volunteers and found that there was a significant correlation between the characteristic peak alpha frequency and the subjective sensation of tonic pain. Jensen et al. found that the specific patterns of changes in the four EEG frequency bands (δ, θ, α, and β) are correlated to pain symptoms in patients with chronic pain due to spinal cord injury. The newest study found that, based on the acquisition of the original EEG signal, using wavelet transform (discrete wavelet transform) to analyze EEG data, might be used to reflect the degree of chronic pain in humans. However, the above studies only remain at the level of theoretical research, and do not yet form a convenient and reliable quantitative indicator for clinical practice.

Pi (range 0–100) is an objective and quantitative EEG pain assessment indicator developed by Chinese researchers in July 2015. The principle of this method is to collect the EEG signals from the prefrontal lobe, using two channels - left and right - and further extract the pain component in the signals. Its corresponding relationship with the VAS/NRS scale is as follows: (1) Pi <10, no pain, corresponding to VAS scale 0–2; (2) Pi = 10–15, pain threshold range, due to different individual pain thresholds, some people can feel pain, some people feel no pain, corresponding to VAS scale 3–4; 3) Pi = 16–30, moderate pain, corresponding to VAS scale 5–7; (4) Pi >30, severe pain, corresponding to VAS scale 8–10. In this study, the monitoring equipment used to collect EEG signals for Pi analysis was HXD-I, which has been widely used in the field of anesthesia and sedation monitoring. This EEG monitoring device only collects left and right two-channel EEG signals from the prefrontal lobe, therefore compared with the traditional standard-channel EEG, this device is more convenient and more efficient in the clinical application.

This study found that Pi values in patients with subjective pain symptoms were significantly higher than those of the healthy volunteers, and the increase in Pi and the increase in subjective VAS/NRS score have a good correlation, suggesting that Pi has value in determining the existence of subjective pain. This study found that an EEG indicator can be used to reflect pain, providing further research and application value for objective quantitative pain assessment. At the same time, we found that the Pi and VAS/NRS scores were independently and significantly correlated after adjusting for type of pain, location of pain, medicaiton, age, sex, and other factors by multivariate stepwise linear regression, suggesting Pi is suitable for patients with different types of pain, different locations of pain and different treatment regimens, and is applicable to pain patients of all ages and both sexes, greatly expanding the application Pi in the future.

This study was an exploratory single-center study that did not further show the temporal relationship between the onset and duration of pain symptoms and the real-time changes in Pi levels, the effect of different types of pain on the Pi index, and the effect of the Pi index on different pain regimens, the timeliness, precision and effectiveness of using Pi to assess patients’ subjective pain symptoms. It is, therefore, necessary to use well-designed multi-center clinical trials to evaluate the application value of Pi. In addition, the study we cannot distinguish between the nature of pain, such as sharp pain, we will conduct a multi-center study to explore the nature of pain.

In summary, the current study confirmed that Pi, based on EEG wavelet algorithm, as a noninvasive, easy-to-use EEG monitoring indicator can reflect the existence and the severity of patients’ subjective pain symptoms. Pi might be used in the future to guide clinicians to be free from the predicament of having to rely on clinical experience and complaints of patients to determine the need for analgesic treatment in patients, and thus promoting the reasonable use of clinical analgesic drugs as well as improving analgesic efficacy.

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Conflicts of interest
There are no conflicts of interest.

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