Patient Education and Counseling 102 (2019) 134–138

Contents lists available at ScienceDirect

Patient Education and Counseling

journal homepage: www.elsevier.com/locate/pateducou

Pain in tones – Is it possible to hear the pain quality? A pilot trial

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ARTICLE INFO

Article history:
Received 24 January 2018
Received in revised form 15 June 2018
Accepted 10 August 2018

Keywords:
Chronic pain
Pain quality
Pain characteristic
Neuropathic pain
Nociceptive pain

ABSTRACT

Objective: The adequate treatment of chronic pain also calls for measuring its quality not only its intensity. For this reason, this pilot study investigated the non-verbal description of pain quality based on tones, distinguishing between nociceptive and neuropathic pain.
Methods: A nociceptive and a neuropathic pain stimulus were applied to 80 chronic pain patients and 80 healthy subjects. Using a tone generator, all participants matched both pain stimuli to an appropriate tone (in Hz). The stimulus intensity was measured using the NRS-scale, and the PainDETECT questionnaire was completed.
Results: Both groups matched a significantly higher tone to the neuropathic than to the nociceptive pain stimulus. Compared to healthy participants, chronic pain patients allocated higher tones to both pain stimuli. Higher values were also shown for the neuropathic pain stimulus, and chronic pain patients indicated an overall higher intensity of pain as healthy participants.
Conclusions: It is possible to differentiate pain stimuli non-verbally through tones, however, whether quality or intensity, was the key factor remains unknown. Future studies could investigate the influence of additional factors.
Practical Implications: A practical tool using tones should be developed to detect pain quality in patients – without verbal descriptions - quickly and more precisely.

1. Introduction

Chronic pain is widespread in the population. Approximately every fifth patient in Germany who is treated by a general practitioner suffers from pain [1]. Acute pain is a sensible alarm signal of the body to avoid tissue damage. It is limited temporally and locally and mostly has a clear underlying cause. The pain intensity depends on the stimulus intensity and usually the pain abates by healing or eliminating the underlying cause. If the pain persists for more than three months, it can become chronic. Chronic pain is defined as persisting pain although the therapy of the injury or disease is completed. Chronic pain recurs, can have many causes and often isn't clearly locatable. Given the complex interaction between objective detectable organic damage and the subjective impairment caused by pain, it is not always easy to initiate adequate treatment. Moreover, those affected often have comorbid psychiatric conditions (mainly depressive disorders) that could additionally complicate the course of treatment. Chronic pain also goes along with severe socioeconomic effects, impairment of accomplishing everyday demands of life and life satisfaction, a reduced level of activity as well as high absences from work possibly resulting in unemployment and the risk of early retirement. This, in return, produces high costs for the health care system [2–4]. For these reasons, it seems very important to meet a decision as early as possible to start treatment. In order to do this, it is not only relevant to measure the intensity of pain but also the quality of pain. A distinction is made between nociceptive and neuropathic pain [5]: nociceptive pain originates from tissue irritation – nerve damage does not exist. Depending on the underlying illness, the quality of pain can vary substantially. Examples of nociceptive pain are arthrosis and pain caused by ischemia. By contrast, neuropathic pain is caused by damage to nerves and is typically described as a sudden, shooting, burning pain that comes abruptly. Neuralgia and ischialgia are examples for neuropathic pain. In order to treat chronic pain overall, an individual treatment plan has to be made, taking the goals of the

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https://doi.org/10.1016/j.pec.2018.08.017
0738-3991/

patient into account. The treatment plan comprises pain reduction, reduction of analgesics consumption and the following improvements: life quality, function, mood, private, professional and social participation. The measures taken to achieve these goals are: physiotherapy, functional training, physical therapy, psychotherapy, relaxation and stress management methods as well as support groups, rehabilitation clinics and advices on social law [5]. Treatment interventions, that are based on specific pain mechanisms, as opposed to the assumption of pain as a uniform phenomenon, give us the opportunity to develop an individualized treatment concept for every patient. Whether a patient suffers from nociceptive or neuropathic pain, plays an important role in the medical treatment and therefore determines the therapeutic success of treatment [5].

The medicinal treatment of nociceptive pain is based on the international step scheme by the World Health Organisation (WHO): simple analgesics, NSAIDs, weak opioids, strong opioids. To treat neuropathic pain anticonvulsants, antidepressants, longer acting opioids and lidocaine or capsaicin patches should be used [5]. In daily clinical practice, the difference between nociceptive or neuropathic pain is mostly made by the patient's own subjective verbal description of the pain. This description is supplemented through standardized questionnaires about the measurement of the quality of pain, i.e. PainDETECT "[3]. However, completing the pertinent questionnaire takes time and requires the use of language in order to describe the pain – which is not so easy for many of the patients. In our experience at clinical practice, native speakers as well as non-native speakers often have difficulties putting their pain into words. Even if they have basic language skills, the specific differentiation between the given terms to describe their pain precisely is too difficult for them. Out of these experiences in our daily practice, the idea grew to develop an appropriate, additional tool, which helps to differentiate between the pain qualities, quickly and without the use of language, based on different frequencies. Regarding the relevance of the quality of pain for treatment, this tool allows a non-verbal assessment of the quality of pain – possibly analog to the Numerical Rating Scale (NRS) and the Visual Analog Scale (VAS) that are used to define intensity of pain and are able to repeatedly document its effectiveness [6]. Our study focuses on the assessment of pain quality. Treatment interventions that are based on specific pain mechanisms give us the opportunity to develop an individualized treatment concept for every patient. This implies that determining pain quality is beneficial in that it improves the success of the treatment [3]. However, the terms used by us aren't to be seen as absolute – they should be a practical tool for the providers. In this pilot study, the hypothesis was tested for the first time, whether chronic pain patients and healthy control subjects could allocate nociceptive and neuropathic pain to very different tones in a defined frequency range (10 Hz–25.000 Hz). If this succeeds, it could be the basis to develop an additional tool for clinical practice in a next step which could identify the quality of pain quickly, reliable, and without the use of speech.

2. Methods

2.1. Procedure

This investigation was performed with permission of the Ethics Committee of the Saarland Medical Chamber, Faktoreistrasse 4 in 66111 Saarbrücken, Germany, ID No. 129/15. First, all subjects filled out a PainDETECT questionnaire and answered several questions about medical history. Then, their blood pressure was measured and the individual participant's hearing range was documented. Afterwards, both tests were followed by the induction of the nociceptive pain stimulus by means of an Esmarch Bandage and a blood pressure cuff and the induction of the neuropathic pain stimulus by means of a TENS (transcutane nerve stimulation) device. The neuropathic pain stimulus was always presented first.

2.2. Participants

After information about the procedure and performance of this study, 80 chronic pain patients and 80 healthy subjects gave their consent to participate in this investigation in the outpatient pain department of the Saarland University Medical Center in Homburg, Germany. All subjects were included who were of legal age and showed no history of deafness nor had other hearing impairments. Furthermore, the following exclusion criteria were implemented: CRPS and damage to the plexus brachialis, PAOD (peripheral artery occlusive disease), tinnitus, systolic blood pressure of >180 mmHg at start of the study, persons with pacemakers and/or defibrillators and persons who met the exclusion criteria for the use of a blood pressure cuff.

2.3. PainDETECT questionnaire

The PainDETECT questionnaire was applied to document the current sensation of pain [3]. This questionnaire is a reliable screening tool to analyze the probability of the presence of neuropathic pain. It includes questions about pain intensity (VAS Scale: current pain, most severe pain in the last four weeks, and the average pain level in the last four weeks), a pictorial description of the patterns of pain, general localization of pain and, if applicable, the radiation of pain (through drawing a mark on the pain stick figure") as well as the quality of pain and –intensity (total of seven questions). This resulted in a total amount that can be classified in the following ranges: with scores between 0 and 13, neuropathic pain is unlikely (<15%), scores between 13 and 19 mean a clear indication is not possible, with scores between 19 and 38, neuropathic pain is highly probable (>90%).

2.4. Medical history, blood pressure measurement, and documentation of hearing range per tone generator

In addition, age and gender were documented at the beginning of the investigation as well as the following questions: Do you suffer from chronic pain? "If yes, are you currently undergoing treatment?", and Which medication are you currently taking?" Also, the patient's blood pressure was measured using a commercially available blood pressure monitor. The individual hearing range was identified by an App, called Tongenerator "by Lifegrit for Apple Products with the iOS operating system which was installed on the Smartphone of the investigator. The frequency range (in Hz) from 10 to 25.000 Hz refers merely to the maximum range that is used to process the tones which is offered by the App. Because the human hearing range is a little smaller and differs individually, the individual hearing range had to be determined for each participant. Every participant states from which frequency range he could hear a tone and from which frequency range he could not hear a tone any more. The equivalence of the indicated frequency with that of the smartphone generated tone was tested and confirmed by the Center for Integrative Physiology and Molecular Medicine (CIPMM) at the University of Saarland.

2.5. Induction of nociceptive pain stimulus

To induce a nociceptive pain stimulus, an Esmarch bandage was wrapped around the patient's arm from the hand to the distal third of the upper arm. A blood pressure cuff was put on the same upper arm and inflated to 250 mmHg for at least two minutes [7,8]. The intensity of pain was assessed using the NRS scale of a slider and

the indicated number was noted by the investigator. Also, the subject was asked to verbally describe the following perceptions of the pain (even if unknown to the investigator if they applied to the subject or not): dull, squeezing, burning, piercing, pulling, tingling, stabbing. Afterwards, the previously defined frequency range was played for the subject, and the subject was asked to specify when the heard frequency measured up to the quality of the pain stimulus.

2.6. Induction of neuropathic pain stimulus

Due to ethical guidelines we obviously couldn't cause a nerve damage to induce neuropathic pain. Therefore we followed the hypothesis of Olesen et al. and used a TENS device with two electrodes, that were put on the contralateral, distal end of the forearm (ventral side), in order to induce a neuropathic-like pain stimulus [7,9]. First the individual pain threshold was determined, afterwards, the pain stimulus was measured (pulse duration 200uS, puls rate 150, a pain level higher than the previously measured personal pain threshold). Analog to the implementation of the induction of nociceptive pain, the intensity of pain and the verbal description of the pain stimulus as well as the frequency that correlated to the quality of the subject's pain stimulus were recorded.

2.7. Statistics

There were no known similar preliminary studies for the present scientific research question, therefore an estimated sample size for this a priori pilot study was not possible.

A Mann–Whitney U test was applied to detect possible group differences regarding age for the descriptive data analysis. Regarding gender, a Chi-squared test was applied; regarding the VAS score, a Mann-Whitney U test was applied, although in this case, a significant difference may be concluded because the VAS score reliably distinguishes between pain patients and healthy subjects. Afterwards, a Wilcoxon test was performed in order to investigate if there is a significant difference in the defined frequency depending on the pain stimulus per test person. This took place in both groups (healthy- and pain patients) as well as for each group separately. Based on the descriptive, clearly observed, substantial difference of the average values of age of both groups, a linear regression analysis was performed in order to evaluate the possible influence of age. For this purpose, a linear regression analysis was performed with a dependent variable frequency in nociceptive pain and in the independent variable group. In a subsequent analysis, age was added as a further independent variable. Both analyses were also carried out with the dependent variable frequency in neuropathic pain. Bootstrapping with a sample size of 10,000 was performed in all analyses of linear regression, and for the determination of the confidence intervals, the BCa method was applied. The bootstrapped regression coefficients as well as the confidence intervals were compared. Considering the mean values and the intensity of pain that was measured by the NRS scale per pain stimuli and group, a Wilcoxon-Test was performed to investigate if a significant difference exists between the intensity of pain pro subject depending on the pain stimulus. This evaluation was made for the group of pain patients as well as for the group of healthy subjects. The risks in terms of an alpha-error accumulation through multiple tests and the consequently possible resulting mistakes were taken into consideration; all following reported statistical significant p-values remain statistically highly significant even after adjustment based on Holm. All statistical evaluations were made with the software package IBM SPSS Statistics 23 "for Windows. An error probability of $p \leq .05$ as a significance level was accepted for all results.

Table 1
Sociodemographic and clinical characteristics of the test groups as well as of the total samples.

Characteristic	Total samples	Pain patients	Healthy subjects	p-Wert
n	160	80	80	–
Age in years	36,0[a]	57,5[a]	24,0[a]	<.001
female (%)	76	70	81	.14
VAS-Score	0,75[a]	3,00[a]	0,00[a]	<.001

a. Median.

3. Results

The demographical data is indicated in Table 1; the distribution of the various qualities of pain is shown in Table 2. The healthy subjects were significantly younger than the pain patients (z = -10,52, $p <$ .001). With regard to the gender, no difference was shown between the test groups (χ^2 (1, N = 160) = 2,75, p = .14). Whereas, in terms of the VAS score, pain patients indicated significantly higher pain levels in a relaxed setting than healthy subjects (z = -10,40, $p <$ .001).

A significantly lower frequency was matched to the nociceptive pain stimulus throughout the entire sampling as to the neuropathic pain stimulus (T(160), z = -8,32, p < .001). The same results were also seen in the group of pain patients (T(80), z = -6,59, p < .001) as well as in the group of healthy subjects (T(80), z = -5,13, p < .001). The median and the corresponding interquartile range of the frequency per pain stimulus and group are shown in Table 3.

An average difference of the groups of β = 93,69 (BCa-confidence interval: -146,34–432,93) was indicated for the nociceptive pain stimulus and adjusted for the age of the participants; a difference of β = 46,60 was shown between the groups (BCa- confidence interval: -304,40–513,04). For the neuropathic pain stimulus, an average difference of the groups of β = −244,64 (BCa- confidence interval: -494,26–8,54) was shown, and adjusted for the age, a difference of β = 46,60 (BCa- confidence interval: -304,40–513,04) was indicated. Since the value 0 in all calculations is included in the confidence interval, we assume that there is no significant influence of age on the outcome.

As shown in Table 4, regarding the median of intensity of pain, a significantly higher reported intensity of the neuropathic pain stimulus compared to the nociceptive pain stimulus was shown in the group of pain patients (T(80), z = -4,73, p < .001) as well as in the group of healthy subjects (T(80), z = -4,42, p < .001).

a. Median, b. Interquartile range

4. Discussion and conclusion

4.1. Discussion

The results show that it is possible to differentiate between two different pain stimuli based on tones. Pain patients as well as healthy subjects were able to match the nociceptive and the neuropathic pain stimulus to significantly different independent frequencies. Regarding the median of the frequency, it is shown that nociceptive pain in both groups is matched to a lower frequency range than the neuropathic pain; that signifies that

Table 2
Presence of various pain qualities in both groups documented in the PainDETECT questionnaire.

	Pain patients	Healthy subjects
Nociceptive pain	43 %	14 %
Neuropathic pain	26 %	0 %
Unclear or mixed pain	31 %	0 %
No pain	0 %	86 %

Table 3
Median of the allocated frequency (Hz) per group (pain patients and healthy subjects) respective of the pain stimulus (nociceptive and neuropathic).

	Nociceptive pain stimulus	Neuropathic pain stimulus	p-Value
Pain patients	528,50 [a], 398,0–649,3 [b]	724,50 [a], 557,0–973,8[b]	<.001
Healthy subjects	351,00 [a], 291,8–453,0[b]	531,50 [a], 417,8–688,3[b]	<.001

a. Median, b. Interquartile range.

Table 4
Median of the allocated pain level (NRS scale) per group (pain patients and healthy subjects) respective of the pain stimulus (nociceptive and neuropathic).

	Nociceptive pain stimulus	Neuropathic pain stimulus	p-Value
Pain patients	5,5[a] 3,0–7,0[b]	7,0[a] 5,0–8,0[b]	< .001
Healthy subjects	3,0[a] 2,0–4,0[b]	4,0[a] 3,0–6,4[b]	< .001

compared to nociceptive pain, neuropathic pain was always associated with a higher tone in the present analysis. This provides initial support for our attempt to be able to differentiate pain through a tone and conversely be able to distinguish between various pain stimuli on this basis.

Concerning the median values of the matched frequencies per group, it is shown that consistently in both groups, the nociceptive pain was matched to a deeper tone. At the same time however, it is observed that the matched frequency in the group of pain patients is higher than that of the healthy subjects. This means that pain patients generally match higher tones to pain than healthy subjects. Various influence factors may play a role here. One could suppose that chronic pain patients perceive pain differently, and consequently depict a tone differently. This assumption is compatible with the fact that patients with different chronic pain syndromes report higher intensity of pain and also show a higher neural reaction to the intensity of pain in clinical studies after experimentally induced pain stimuli compared to healthy control subjects [10–15]. Furthermore, Bushnell, Čeko, and Low [16] postulate in their review that in chronic pain patients, functional changes occur all the way to degenerative processes in areas of the brain which regulate the cognitive processes of analgesia. Moreover, age could have also played a role. Even though we could overrule the influence of age on the examined effect as not significant, nevertheless, the general upward shift of chosen frequencies in the group of pain patients could be owed to the average higher age in this group. It is commonly known that hearing ability diminishes with increasing age and that aging in relation to hearing ability is accompanied with morphometric and chemical as well as functional changes in the brain [17]. In addition, a correlation between age and perception of pain is possible. There is evidence that age-related changes in pain perception matter [18–20], even though these changes appear to be very complex so that a certain direction of change cannot simply be concluded [21]. Other changes include the rising amount of comorbidities with age as well as the influence of geriatric syndromes which are accompanied by a complex interaction of the perception of pain [21,22]. The reason why the matched frequencies of the pain patients generally lie in a higher frequency range as that of the healthy subjects cannot be conclusively clarified at this point and requires further research.

Concerning the frequencies there is a transition area of frequencies, which cannot be clearly assigned to nociceptive or neuropathic pain. This may support the theoretical idea of neuropathic and nociceptive pain being the two ends of one continuum [23] and matches the scale of the PainDETECT questionnaire as well [3]. One can have both pain types at one time and there is a transition area where you cannot unambiguously correlate the afflictions to one or the other side. Concurrently muscle pain can be so severe, that it is described as" burning" – however it isn't only because of the description that the muscle pain consequently becomes neuropathic pain.

Regarding the perceived pain intensity, a difference is shown between nociceptive and neuropathic pain stimuli. Neuropathic pain is experienced as significantly stronger than nociceptive pain in both groups. Considering the median per group and induced pain stimulus, it is noticeable that, similar to the allocation of the corresponding frequencies, the pain patients ascribe both pain stimuli to higher pain intensity than healthy patients. Consequently, based on the results, it cannot be concluded with certainty that the difference in the quality of pain for a successful differentiation of pain stimuli is causally based on tones since the difference in the intensity of pain could have at least partly influenced this association. Therefore the question still remains if both groups could still reliably distinguish between both pain stimuli based on tones in two induced pain stimuli with different qualities yet the same intensity. A probable cause for the deviating intensities of pain might lie in the method of induction and its accuracy of measurement. Turk, Rudy, and Sorkin [24] have previously emphasized the importance of the assessment of reliability in the chosen pain measurement methods as well as Beecher [25] emphasizes the necessity of controlled double-blind-studies and the consideration of emotional components in the measurement of pain to rule out as many sources of error in the methods as possible. According to Maurischat [7], diverse sources of errors could already occur in comparing one and the same method of pain induction such as through the inaccuracy of the measuring tools themselves (e.g. due to a lack of technology) or changing of testing conditions (fatigue of the test person, behavior of the investigator, sensitivities depending on the daily form) which lead to diverse results. In his study, the reliability in measuring ischemia pain could be shown even when the absolute height of the pain threshold in both experiments differed substantially. He attributed the differences in pain intensity to the differences in the experimental procedures. The sequence of the pain induction could also have had an influence on the perception of pain intensity. The nociceptive pain stimulus was always presented first, followed by the neuropathic pain stimulus. The results of the groups 'differences in the intensity of pain correspond with the results of the matching frequencies: In comparison to the healthy patients, the pain patients associated both stimuli with higher frequencies and with stronger intensities of pain. Here again, differences in the perception of pain and influence of age as well as complex interactions between both factors are possible.

Regarding the frequency of the corresponding verbal description to the pain stimuli, it can be assumed that both groups could report about the difference of pain quality not only tonal but verbally. More than 50 percent of the subjects described the nociceptive pain stimulus as dull, pressing, and tingling; by contrast, the neuropathic pain stimulus was described as stabbing, pulling, tingling, and piercing. In the translation of pain conditions in tones, it could be assumed that musicians might succeed more

precisely. One prominent example of this is Wagner who, in the first act of Siegfried's opera, set his suffering of migraines to music [26]. In a follow-up study, one could perhaps work together with a musician who could set both pain stimuli to music and then examine if this makes an even better distinction possible.

There are, however, some limitations. First, the method of induction of both pain stimuli and the assessment of the stimuli as nociceptive and neuropathic pain can be criticized since the indicated intensity of pain in both test groups is stronger for that which is considered a neuropathic pain stimulus. Possibly the intensity of both stimuli varies and they are not suitable for this type of comparison of the pain quality. Nonetheless, if the verbal description of the pain stimuli about the frequency of each applicable, selected term is assessed, one can assume that the different quality of pain would definitely be detected by the test groups. Furthermore, the missing counterbalance of the presentation of the two pain stimuli could have had an influence on the perception of the pain. It could be taken into account for the fact, that the second pain stimuli (neuropathic pain) was perceived higher in intensity. Maybe the effect of increased anxiety after application of the first stimuli could have played a role. Also, the characteristics of both test groups should be taken into account. The significant difference in age was in fact corrected in the statistical evaluation and did not show a significant influence in this study on the effect; nevertheless, in future studies, it would seem to be reasonable to examine the influence of age in advance. On the one hand, due to the reduction of hearing performance in old age [17], on the other hand, due to the likely very complex interaction between pain perception and age [18–22]. For this purpose, several age groups of pain patients with respective groups of healthy subjects could be compared in terms of their allocation of frequencies to both pain stimuli. At the same time, the perception of pain in the individual groups and their relation to age could be examined more closely.

4.2. Conclusion

Overall, one can conclude that pain patients as well as healthy patients were capable of differentiating pain stimuli by associating them with tones. Nevertheless, based on the current data, it couldn't be adequately explained which characteristic of pain (intensity or quality) was the decisive factor. For future research it would therefore be relevant to initially define two qualitative different pain stimuli with equal intensity in order to answer this question. There is also a need to verify in pain patients as well as in healthy subjects which factors influence the determination of tones. For this purpose, a detailed analysis of different age groups would seem to be useful. Furthermore, the possible differences in the perception of pain should also be examined in the test groups.

Authors contributions

Patric Bialas was the chief investigator. He was responsible for trial design, data interpretation and writing of the manuscript. Both authors conducted equally to the paper.

Benjamin Gronwald was responsible for trial design, data analysis and statistical analysis.

Sven Gottschling was responsible for data analysis and manuscript preparation.

Kati Roloff was responsible for data analysis and manuscript preparation.

Svenja Kreutzer was responsible for data analysis, manuscript preparation and writing.

Katja Welsch She was responsible for data analysis and manuscript preparation.

Thomas Volk He was responsible for trial design, data analysis and writing of the manuscript.

All Authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflictsof interests

The Authors have no conflicts of interests to disclose relevant to this article

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