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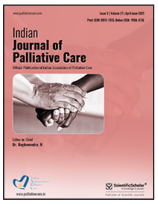

General Medicine *Review Article*

Non-Invasive Objective Markers to Measure Pain: A Direction to Develop a Pain Device - A Narrative Review

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ABSTRACT

Objective: To review the literature regarding non-invasive objective measurements of pain. Measuring pain is of uttermost importance, but it can be an inconvenient task, especially in terms of the interpretation of patient's information. Reiterating, there is no "standard" that provides the physician with a method to objectively quantify this problem of patient's pain. For assessing the pain, physician relies solely on unidimensional assessment tools or questionnaire-based pain assessment. Although pain is a subjective experience of the patient, but there is a need to measure pain sometimes in the individuals who cannot communicate their quality and severity of pain.

Material and Methods: The articles from PubMed and Google Scholar without any year and age limit were searched in the current narrative review. A total of 16 markers were searched and their relation to pain was studied.

Results: Studies have shown that these markers change in relation to pain and it can be considered a valuable tool for pain measurement but there are multiple factors like psychological and emotional factors which affect these markers.

Conclusion: There is lack of evidence to show which marker can be used for measuring pain accurately. This narrative review is an attempt to look into the various pain-related markers that can be used and it calls for further studies including clinical trials with different diseases and taking into accounts different factors affecting pain to give an accurate measurement of pain.

Keywords: Pain, Non-invasive, Markers, Objective assessment

INTRODUCTION

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.[1] Most of the patients requiring palliative care undergo profound suffering with severe pain and most of these patients require opioids. Palliative care physician has a major role to alleviate such suffering. There is always a dilemma with palliative care physicians while prescribing opioids, thinking about dependence and addiction. The pain is currently being measured subjectively and current pain assessment questionnaires rely on scoring given by the patient, requiring the patient's physical condition reporting and also his social and psychological experience. The objective method of pain measurement would utilise the various markers but there are several shortcomings to trusting these markers.

To measure pain objectively, the tool needs to have high sensitivity and specificity to pain. Looking at all the issues while prescribing opioids, the need to develop a device to measure pain objectively is the need of the hour.

Objective

This narrative review article will be a step forward to see the available current evidence about different pain-related markers for possible future development of pain devices.

MATERIAL AND METHODS

The narrative review was conducted using PubMed and Google Scholar electronic databases. The keywords searched were 'nerve conduction velocity' AND 'pain,' 'NCV' AND 'pain,' 'galvanic skin response' AND 'pain,' 'GSR' AND 'pain,' 'heart rate' AND 'pain,' 'pulse' AND 'pain,' 'blood pressure'

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AND 'pain,' 'electroencephalogram' AND 'pain,' 'EEG' AND 'pain,' 'respiratory rate' AND 'pain,' 'oxygen saturation' AND 'pain,' 'surgical plethysmographic index' AND 'pain,' 'electromyography' AND 'pain,' 'EMG' AND 'pain,' 'pupillary diameter' AND 'pain,' 'body temperature' AND 'pain' and 'saliva biomarkers' AND 'pain.'

The articles were included for further analysis if the title or the abstract showed the matching keywords. We decided not to specify a year range for the selection of articles. The articles were excluded if they contained only abstracts, were not in the English language, and studies published in conferences, books, or book chapters were also excluded. We also searched further from the references of the articles which showed our area of concern.

DISCUSSION

Assessing pain objectively is always challenging and extensive research should be done to develop a way to measure pain accurately. Although pain is defined as a subjective experience, we studied markers related to pain in the current narrative review which can be used to measure pain objectively. The searched pain-related markers are listed in [Table 1].

Salivary biomarkers

The salivary glands contain various pain-associated biomarkers and they are connected to the neuroendocrine system.[2] Studies have reported a correlation between salivary concentrations of biomarkers and pain. The substances P and glutamate are the most important neurotransmitters responsible for pain transmission and are present in saliva.[3,4] Salivary concentration of substance P was significantly correlated with dental pain. The substance P level was higher in patients who had dental pain compared with patients who had no dental pain.[5] High level of substance P and Glutamate in saliva has been reported in patients having high-intensity chronic migraine pain.[6] High concentration of glutamate production within the posterior insula causes enhanced glutaminergic neurotransmission and this correlates with individual pain sensitivity and this may contribute a part to the pathophysiology of Fibromyalgia and central pain augmentation syndrome.[7] It has been seen in a previous study that the level of saliva cortisol is directly associated with osteoarthritis related pain. The increased level of cortisol has been seen in women with greater pain severity.[8] Self pain perception and salivary cortisol had a positive correlation in a study done by Alresayes *et al*. in adolescents with temporomandibular disorder.[9] The salivary alpha amylases also correlate significantly with pain. Vahedi *et al*. reported that salivary alpha amylase concentration was significantly higher in patients with a headache when compared with control patients.[10] A positive correlation has been shown in studies between salivary a-amylase and pain level in patients who were posted for surgery before and after.[11,12] Studies have shown that secretory IgA (sIgA) levels may interfere with the pain experienced by the patient and it may have a negative correlation with pain.[13] Both soluble tumour necrosis factor-α receptor II (sTNF-RII) and sIgA can be a reliable salivary biomarkers for pain assessment but sTNF-RII can be more accurate in diagnosing pain in people with advanced dementia.[14] Alpha-amylase and IgA were present in higher amounts in the saliva of a patient with burning mouth syndrome[15] and these markers could be used as pain biomarkers.[16] The studies regarding pain assessment using salivary biomarkers are limited. As saliva is an easily obtained and non-invasive process, this technique could be a good option to assess pain objectively. More research should be focused on developing saliva-based biosensor technology to measure these biomarkers for pain assessment objectively.

Table 1: Pain-related markers depending upon the location.

Location	Markers
Salivary biomarkers	Glutamate, substance P, alpha amylase, cortisol, soluble tumour necrosis factor-α receptor II and secretory IgA
Cardiovascular system	Heart rate variability, blood pressure
Nervous system	Electroencephalography, nerve conduction velocity
Skin	Galvanic skin response
Respiratory	Respiratory rate, oxygen saturation, surgical plethysmographic index
Eye	Pupillary diameter
Musculoskeletal	Electromyography

Heart rate variability (HRV)

HRV is the physiological change in the time interval between heartbeats. Chronic pain produces changes in HRV and this chronic pain is influenced by both the sympathetic and parasympathetic nervous systems. This change in autonomic balance can be measured. The painful stimulation produces changes in time and frequency between successive heartbeats reflecting autonomic reactivity to painful stimulation.[17,18] This is a simple and non-invasive variable that uses standard ECG monitoring and can also be used in both sedated and awake patients.[19,20] However, breathing cycles fluctuates the heart rate and these considerations have improved the parameter accuracy.[21]

Blood pressure (BP)

There is an inverse relationship between acute pain response and BP at rest in normotensive adults and adolescents without pain.[22-26] Many studies reported that patients with chronic pain may have dysfunction of BP and hypoalgesia and this shows absence of inverse relationship between acute pain sensitivity and BP.[27-31] Some studies have shown that there are some changes in descending inhibitory pathways due to chronic pain, for example, α2-

adrenergic, baroreflex sensitivity, and endogenous opioids may be involved in altering the relation between BP and the pain modulatory system.[30,31] Central sensitisation which involves the upregulation of ascending pain pathways may be involved in chronic pain patients.[32]

Electroencephalography (EEG)

EEG device records the electrical activity of the brain. This is a non-invasive technique that uses electrodes that are placed over the scalp. Ionic current produces voltage fluctuations within the brain and this can be measured by EEG.[33] Quantitative EEG has been applied to assess brain functioning in several chronic pain syndromes.[34] The central and peripheral processing of painful input can be reflected by the signal amplitudes in EEG, that correlate with painful stimulus. These measured signal amplitudes are altered by analgesic medication;[35-38] the precision required to know whether the stimulus is painful or non-painful can be debatable.[38-43] At present, promising results have been shown by steady-state evoked potentials which quantify long lasting changes after a period of sensory stimulus and infrared laser evoked potentials,[44-47] although do not show the neural coding of pain intensity.[41] In this situation, a subjective way of pain estimation which is estimated by gamma-band oscillations can be a promising alternative.[48] At present, this way of measuring pain intensity via EEG is within the research setting and it requires careful experimental studies. However, with more clinical research on a larger population, these techniques may help measure pain objectively.

Nerve conduction velocity

The peripheral nervous system is composed of nerve fibres identified as A-beta, A-delta, and C-fibres. The A-delta and C nerve fibres are the main pain-conducting nerve fibres systems.[49] The various approaches to measure the function of pain pathways for A-delta and C-fibres are electrically, mechanically, and thermally. These three sensory tests are called quantitative sensory testing that measures the function of the small nerve fibres.[50] The pathways of the pain are made up of nerves and the pain function could be measured electrically. Kall *et al*. invented an electrical device called Pain-Matcher that allows an objective way of performing pain measurement and provides a measurement value of pain.[51] Many mechanical instruments have been used clinically to measure the function of nerve fibers of pain, that is, Muscle Pain Detection Device and PainTest™ FPX 25 Algometer.[52,53] The nerve A-delta and C-nerve fibres play an important role in pain transmission and temperature sensation. The range of temperature through the device using warm and cold perception threshold can measure the functions of pain.[54] Various devices have been developed for the quantitative thermal sensory nerve pathway testing, that is, CASE IV thermal testing probe, Marstock stimulator, Glasgow system, Middlesex Hospital thermal testing system, PATH-tester MPI 100, Thermal sensory analyser TSA-2001, Painmouse and Thermal sensitivity tester.[55-62]

Galvanic skin response (GSR)

The change in the electrical property of the skin is called GSR. Painful stimuli activate autonomic nervous system which causes sweating and decrease the skin's electrical resistance and thereby its conductance increases. The frequency of skin conductance and amplitude has been measured by various devices. This frequency and amplitude can be used to correlate with pain stimulus.[63] To measure GSR, the constant voltage needs to be applied on a person's skin and the skin conductance is measured with the help of Ohm's Law by calculating the flow of current. Self-adhesive electrodes have to be applied to the palm or sole for measurement. The GSR amplifier delivers a small voltage through the person's skin which is not perceived by humans but amplification can detect the response.[64]

Respiratory rate (RR)

It has been reported in previous studies that the RR was evaluated when pain increases in the animals.[65] A positive correlation between pain intensity and RR was also found in human studies. Many studies have noted that RR increases during the pain and it may be the most frequent physiological indicator of pain.[66,67] Significant changes had been reported in RR during nociceptive procedures. Erden *et al*. observed a positive correlation between RR and pain intensity in patients admitted to the intensive care unit.[68] Dantas *et al*. also reported the same results in children. They reported a significant increase in RR ($P = 0.001$) due to pain.[69]

Oxygen saturation

Oxygen saturation is routinely measured by pulse oximeter and it can slightly vary with physiological changes occurring in the human body. Evaluating oxygen saturation and RR changes can be a valuable tool to measure pain objectively. Measuring pain in neonates or non-verbal patients is a difficult task. The study reported low sensitivity and specificity of oxygen saturation to evaluate neonatal pain and used only as an auxiliary method.[70] Saleh *et al*. reported no statistically significant relationship between oxygen saturation before and after analgesia.[71] Further research on a larger population is required to correlate the association between oxygen saturation and pain assessment and this non-invasive method can be used to measure pain objectively.

Surgical plethysmographic index (SPI)

The device SPI has been used to monitor the hemodynamic responses to analgesic medications and surgical stimuli during anaesthesia. This device records the increased sympathetic activity as a reaction to painful nociceptive stimuli and can be used to assess acute nociceptive stimuli. The mechanism

is based on the photoplethysmographic waveforms of oxygen saturation measurements to analyse pulse wave interval and amplitude. A linear scale number from 0 to 100 is generated and the pain is considered if the values are more than 50.[72] SPI can be useful in predicting postoperative pain, if obtained before patient arousal and correlated significantly with arousal.[73] Thee *et al*. studied the relationship between the numeric rating scale and SPI and a significant correlation with total opioid consumption was found.[74]

Pupillometry

Noxious stimuli can cause sympathetic stimulation which leads to pupillary dilatation. Various devices are used to measure the diameter of the pupil involving the non-invasive infrared principle. These pupillary responses could be influenced by several other factors such as drugs, environmental luminance, age, and other disease conditions.[75,76] However these pupillary changes could be an important marker to analyse pain in non-verbal patients and neonates. Pupillometry has been reported as a technique to assess the pain objectively and to assess the pharmacodynamics of opioids.[77,78] The nociceptive signal through autonomic innervations of iris muscles can be detected by pupil dilatation extension and the pharmacological effect in the central nervous system is provided by attenuation extension in pupillary response during opioid exposure.[79]

Electromyography

Electromyography is a device to measure the response of the muscle to a nerve's stimulation and has been used as an alternative method for the assessment of muscular pain.[80] Gruss *et al*. used the EMG as one of the markers of a physiological signal to measure pain intensity.[81] Candotti *et al*. reported a significant difference between the enrolled population with pain and no pain in the upper trapezius using surface electromyography. The lower force value has been reported in people with pain.[80,82] Ambroz *et al*. outlined a significant correlation between surface electromyography and objective pain assessment in chronic low back pain patients. Muscle activity was threefold higher in these patients with pain when compared to patients without pain. Surface electromyography may be a useful objective diagnostic tool for the assessment of chronic lower back pain.[83] The study reported by Mieronkoski *et al*. used surface electromyography to detect facial expressions during pain.[84]

Limitation

We feel adding more databases could have given more insight into the current narrative review. Critical appraisals about each and every article were not included in this narrative review. Systematic review could have given robust evidence on the current topic. Invasive methods of measuring pain were not considered. Systematic review for future studies on the current topic including all the parameters irrespective of invasive or non-invasive will give concrete evidence to move forward in making a device to measure pain objectively.

CONCLUSION

Pain is almost always measured subjectively and measuring pain objectively can be difficult because of multifactorial causes. There are very limited studies or evidence to show the objective methods of measuring pain. The current narrative review has highlighted the importance of basic markers for the non-invasive measurement of pain. Non-invasive parameters discussed in this study can be a valuable tool to guide future studies.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, *et al*. The revised International Association for the Study of Pain definition of pain: Concepts, challenges, and compromises. Pain 2020;161:1976-82.
2. Mathison R, Davison JS, Befus AD. Neuroendocrine regulation of inflammation and tissue repair by submandibular gland factors. Immunol Today 1994;15:527-32.
3. D'Mello R, Dickenson AH. Spinal cord mechanisms of pain. Br J Anaesth 2008;101:8-16.
4. Jasim H, Carlsson A, Hedenberg-Magnusson B, Ghafouri B, Ernberg M. Saliva as a medium to detect and measure biomarkers related to pain. Sci Rep 2018;8:3220.
5. Ahmad M, Williams J, Al-Abbousi R, Wheater M. Substance P concentration in saliva of patients who report dental pain. J Adv Oral Res 2014;5:1-5.
6. Jang MU, Park JW, Kho HS, Chung SC, Chung JW. Plasma and saliva levels of nerve growth factor and neuropeptides in chronic migraine patients. Oral Dis 2011;17:187-93.
7. Zunhammer M, Schweizer LM, Witte V, Harris RE, Bingel U, Schmidt-Wilcke T. Combined glutamate and glutamine levels in pain-processing brain regions are associated with individual pain sensitivity. Pain 2016;157:2248-56.
8. Carlesso LC, Sturgeon JA, Zautra AJ. Exploring the relationship between disease-related pain and cortisol levels in women with osteoarthritis. Osteoarthritis Cartilage 2016;24:2048-54.
9. Alresayes S, Al-Aali K, Javed F, Alghamdi O, Mokeem SA, Vohra F, *et al*. Assessment of self-rated pain perception and whole salivary cortisol levels among adolescents with and without temporomandibular disorders. Cranio 2021:1-7. DOI: 10.1080/08869634.2021.1899697.
10. Vahedi M, Mazdeh M, Hajilooi M, Farhadian M, Barakian Y, Sadr P. The relationship between salivary alpha amylase activity and score of McGill pain questionnaire in patients with tension type headache. Basic Clin Neurosci 2018;9:59-64.
11. Surin W, Chatiketu P, Hutachok N, Srichairatanakool S, Chatupos V. Pain intensity and salivary α-amylase activity in patients following mandibular third molar surgery. Clin Exp Dent Res 2022;8:1082-91.
12. Shirasaki S, Fujii H, Takahashi M, Sato T, Ebina M, Noto Y, *et al*. Correlation

between salivary alpha-amylase activity and pain scale in patients with chronic pain. Reg Anesth Pain Med 2007;32:120-3.
13. da Silva Campos MJ, Alves CC, Raposo NR, Ferreira AP, Vitral RW. Influence of salivary secretory immunoglobulin A level on the pain experienced by orthodontic patients. Med Sci Monit 2010;16:CR405-9.
14. Cantón-Habas V, Rich-Ruiz M, Moreno-Casbas MT, Ramírez-Expósito MJ, Martínez-Martos JM, Carrera-González MD. Correlation between biomarkers of pain in saliva and PAINAD Scale in elderly people with cognitive impairment and inability to communicate. J Clin Med 2021;10:1424.
15. Lopez-Jornet P, Felipe CC, Pardo-Marin L, Ceron JJ, Pons-Fuster E, Tvarijonaviciute A. Salivary biomarkers and their correlation with pain and stress in patients with burning mouth syndrome. J Clin Med 2020;9:929.
16. Sobas EM, Reinoso R, Cuadrado-Asensio R, Fernández I, Maldonado MJ, Pastor JC. Reliability of potential pain biomarkers in the saliva of healthy subjects: Inter-individual differences and intersession variability. PLoS One 2016;11:e0166976.
17. Koenig J, Jarczok MN, Ellis RJ, Hillecke TK, Thayer JF. Heart rate variability and experimentally induced pain in healthy adults: A systematic review. Eur J Pain 2014;18:301-14.
18. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: Scientific advances and future directions. Psychol Bull 2007;133:581-624.
19. Mazzeo AT, La Monaca E, Di Leo R, Vita G, Santamaria LB. Heart rate variability: A diagnostic and prognostic tool in anesthesia and intensive care. Acta Anaesthesiol Scand 2011;55:797-811.
20. Kristiansen J, Ektor-Andersen J, Bondesson E, Orbæk P, Persson R, Garde AH, *et al*. Low heart rate variability is associated with extended pain-related sick leave among employed care-seekers. J Rehabil Med 2011;43:976-82.
21. Taylor JA, Myers CW, Halliwill JR, Seidel H, Eckberg DL. Sympathetic restraint of respiratory sinus arrhythmia: Implications for vagal-cardiac tone assessment in humans. Am J Physiol Heart Circ Physiol 2001;280:H2804-14.
22. Bruehl S, Carlson CR, McCubbin JA. The relationship between pain sensitivity and blood pressure in normotensives. Pain 1992;48:463-7.
23. McCubbin JA, Bruehl S. Do endogenous opioids mediate the relationship between blood pressure and pain sensitivity in normotensives? Pain 1994;57:63-7.
24. Page GD, France CR. Objective evidence of decreased pain perception in normotensives at risk for hypertension. Pain 1997;73:173-80.
25. Campbell TS, Ditto B, Séguin JR, Assaad JM, Pihl RO, Nagin D, *et al*. A longitudinal study of pain sensitivity and blood pressure in adolescent boys: Results from a 5-year follow-up. Health Psychol 2002;21:594-600.
26. Ditto B, Séguin JR, Boulerice B, Pihl RO, Tremblay RE. Risk for hypertension and pain sensitivity in adolescent boys. Health Psychol 1998;17:249-54.
27. Bragdon EE, Light KC, Costello NL, Sigurdsson A, Bunting S, Bhalang K, *et al*. Group differences in pain modulation: Pain-free women compared to pain-free men and to women with TMD. Pain 2002;96:227-7.
28. Bruehl S, Chung OY, Ward P, Johnson B, McCubbin JA. The relationship between resting blood pressure and acute pain sensitivity in healthy normotensives and chronic back pain sufferers: The effects of opioid blockade. Pain 2002;100:191-201.
29. Brody S, Angrilli A, Weiss U, Birbaumer N, Mini A, Veit R, *et al*. Somatotosensory evoked potentials during baroreceptor stimulation in chronic low back pain patients and normal controls. Int J Psychophysiol 1997;25:201-10.
30. Chung OY, Bruehl S, Diedrich L, Diedrich A, Chont M, Robertson D. Baroreflex sensitivity associated hypoalgesia in healthy states is altered by chronic pain. Pain 2008;138:87-97.
31. Maixner W, Fillingim R, Kincaid S, Sigurdsson A, Harris MB. Relationship between pain sensitivity and resting arterial blood pressure in patients with painful temporomandibular disorders. Psychosom Med 1997;59:503-11.
32. Chung OY, Bruehl S. The impact of blood pressure and baroreflex sensitivity on wind-up. Anesth Analg 2008;107:1018-25.
33. Biasiucci A, Franceschiello B, Murray MM. Electroencephalography. Curr Biol 2019;29:R80-5.
34. Stern J, Jeanmonod D, Sarnthein J. Persistent EEG overactivation in the cortical pain matrix of neurogenic pain patients. Neuroimage 2006;31:721-31.
35. Untergehrer G, Jordan D, Eyl S, Schneider G. Effects of propofol, sevoflurane, remifentanil, and (S)-ketamine in subanesthetic concentrations on visceral and somatosensory pain-evoked potentials. Anesthesiology 2013;118:308-17.
36. Iannetti GD, Zambreanu L, Cruccu G, Tracey I. Operculoinsular cortex encodes pain intensity at the earliest stages of cortical processing as indicated by amplitude of laser-evoked potentials in humans. Neuroscience 2005;131:199-208.
37. Lee MC, Mouraux A, Iannetti GD. Characterizing the cortical activity through which pain emerges from nociception. J Neurosci 2009;29:7909-16.
38. Legrain V, Iannetti GD, Plaghki L, Mouraux A. The pain matrix reloaded: A salience detection system for the body. Prog Neurobiol 2011;93:111-24.
39. Iannetti GD, Mouraux A. From the neuromatrix to the pain matrix (and back). Exp Brain Res 2010;205:1-12.
40. Downar J, Crawley AP, Mikulis DJ, Davis KD. A multimodal cortical network for the detection of changes in the sensory environment. Nat Neurosci 2000;3:277-83.
41. Iannetti GD, Hughes NP, Lee MC, Mouraux A. Determinants of laser-evoked EEG responses: Pain perception or stimulus saliency? J Neurophysiol 2008;100:815-28.
42. Mouraux A, De Paepe AL, Marot E, Plaghki L, Iannetti GD, Legrain V. Unmasking the obligatory components of nociceptive event-related brain potentials. J Neurophysiol 2013;110:2312-24.
43. Mouraux A, Iannetti GD. Nociceptive laser-evoked brain potentials do not reflect nociceptive-specific neural activity. J Neurophysiol 2009;101:3258-69.
44. Huang G, Xiao P, Hung YS, Iannetti GD, Zhang ZG, Hu L. A novel approach to predict subjective pain perception from single-trial laser-evoked potentials. Neuroimage 2013;81:283-93.
45. Mouraux A, Iannetti GD, Colon E, Nozaradan S, Legrain V, Plaghki L. Nociceptive steady-state evoked potentials elicited by rapid periodic thermal stimulation of cutaneous nociceptors. J Neurosci 2011;31:6079-87.
46. Colon E, Legrain V, Mouraux A. Steady-state evoked potentials to study the processing of tactile and nociceptive somatosensory input in the human brain. Neurophysiol Clin 2012;42:315-23.
47. Iannetti GD, Leandri M, Truini A, Zambreanu L, Cruccu G, Tracey I. Adelta nociceptor response to laser stimuli: Selective effect of stimulus duration on skin temperature, brain potentials and pain perception. Clin Neurophysiol 2004;115:2629-37.
48. Zhang ZG, Hu L, Hung YS, Mouraux A, Iannetti GD. Gamma-band oscillations in the primary somatosensory cortex--a direct and obligatory correlate of subjective pain intensity. J Neurosci 2012;32:7429-38.
49. Beissner F, Brandau A, Henke C, Felden L, Baumgärtner U, Treede RD, *et al*. Quick discrimination of A(delta) and C fiber mediated pain based on three verbal descriptors. PLoS One 2010;5:e12944.
50. Krumova EK, Geber C, Westermann A, Maier C. Neuropathic pain: Is quantitative sensory testing helpful? Curr Diab Rep 2012;12:393-402.
51. Kall LB, Kowalski J, Stener-Victorin E. Assessing pain perception using the Painmatcher in patients with whiplash-associated disorders. J Rehabil Med 2008;40:171-7.
52. Hunter C, Dubois M, Zou S, Oswald W, Coakley K, Conlon AM. A new muscle pain detection device to diagnose muscles as a source of back and/or neck pain. Pain Med 2010;11:35-43.
53. Buhagiar L, Cassar OA, Brincat MP, Buttigieg GG, Inglott AS, Adami MZ, *et al*. Predictors of post-caesarean section pain and analgesic consumption. J Anaesthesiol Clin Pharmacol 2011;27:185-91.
54. Moloney NA, Hall TM, Doody CM. Reliability of thermal quantitative sensory testing: A systematic review. J Rehabil Res Dev 2012;49:191-207.
55. Fruhstorfer H, Lindblom U, Schmidt WG. Method for quantitative estimation of thermal thresholds in patients. J Neurol Neurosurg Psychiatry 1976;39:1071-5.
56. Backonja MM, Walk D, Edwards RR, Sehgal N, Moeller-Bertram T, Wasan A, *et al*. Quantitative sensory testing in measurement of neuropathic pain phenomena and other sensory abnormalities. Clin J Pain 2009;25:641-7.
57. Bravenboer B, Van Dam PS, Hop J, Vd Steenhoven J, Erkelens DW. Thermal threshold testing for the assessment of small fibre dysfunction: Normal values and reproducibility. Diabet Med 1992;9:546-9.
58. Fowler CJ, Carroll MB, Burns D, Howe N, Robinson K. A portable system for measuring cutaneous thresholds for warming and cooling. J Neurol Neurosurg Psychiatry 1987;50:1211-5.
59. Arezzo JC, Schaumburg HH, Laudadio C. Thermal sensitivity tester.

Device for quantitative assessment of thermal sense in diabetic neuropathy. Diabetes 1986;35:590-2.
60. Grothusen JR, Alexander G, Erwin K, Schwartzman R. Thermal pain in complex regional pain syndrome Type I. Pain Physician 2014;17:71-9.
61. Claus D, Hilz MJ, Neundorfer B. Thermal discrimination thresholds: A comparison of different methods. Acta Neurol Scand 1990;81:533-40.
62. Schaffner N, Folkers G, Käppeli S, Musholt M, Hofbauer GF, Candia V. A new tool for real-time pain assessment in experimental and clinical environments. PLoS One 2012;7:e51014.
63. Storm H. Changes in skin conductance as a tool to monitor nociceptive stimulation and pain. Curr Opin Anaesthesiol 2008;21:796-804.
64. Sharma M, Kacker S, Sharma M. A brief introduction and review on galvanic skin response. Int J Med Res Prof 2016;2:13-7.
65. Gigliuto C, De Gregori M, Malafoglia V, Raffaeli W, Compagnone C, Visai L, *et al*. Pain assessment in animal models: Do we need further studies? J Pain Res 2014;7:227-36.
66. Jafari H, Courtois I, Van den Bergh O, Vlaeyen JW, Van Diest I. Pain and respiration: A systematic review. Pain 2017;158:995-1006.
67. Kabes AM, Graves JK, Norris J. Further validation of the nonverbal pain scale in intensive care patients. Crit Care Nurse 2009;29:59-66.
68. Erden S, Demir N, Ugras GA, Arslan U, Arslan S. Vital signs: Valid indicators to assess pain in intensive care unit patients? An observational, descriptive study. Nurs Health Sci 2018;20:502-8.
69. Dantas LV, Dantas TS, Filho VJ, Azevedo-Santos IF, DeSantana JM. Pain assessment during blood collection from sedated and mechanically ventilated children. Rev Bras Ter Intensiva 2016;28:49-54.
70. Pereira AL, Guinsburg R, De Almeida MF, Monteiro AC, Dos Santos AM, Kopelman BI. Validity of behavioral and physiologic parameters for acute pain assessment of term newborn infants. Sao Paulo Med J 1999;117:72-80.
71. Saleh AN, Mostafa RH, Hamdy AN, Hafez AF. Pulse-oximetry derived perfusion index as a predictor of the efficacy of rescue analgesia after major abdominal surgeries. Open Anes J 2020;14:101-7.
72. Huiku M, Uutela K, Van Gils M, Korhonen I, Kymäläinen M, Meriläinen P, *et al*. Assessment of surgical stress during general anaesthesia. Br J Anaesth 2007;98:447-55.
73. Ledowski T, Burke J, Hruby J. Surgical pleth index: Prediction of postoperative pain and influence of arousal. Br J Anaesth 2016;117:371-4.
74. Thee C, Ilies C, Gruenewald M, Kleinschmidt A, Steinfath M, Bein B. Reliability of the surgical Pleth index for assessment of postoperative pain: A pilot study. Eur J Anaesthesiol 2015;32:44-8.
75. Eilers H, Larson MD. The effect of ketamine and nitrous oxide on the human pupillary light reflex during general anesthesia. Auton Neurosci 2010;152:108-14.
76. Rouche O, Wolak-Thierry A, Destoop Q, Milloncourt L, Floch T, Raclot P, *et al*. Evaluation of the depth of sedation in an intensive care unit based on the photo motor reflex variations measured by video pupillometry. Ann Intensive Care 2013;3:5.
77. Bertrand AL, Garcia JB, Viera EB, Santos AM, Bertrand RH. Pupillometry: The influence of gender and anxiety on the pain response. Pain Physician 2013;16:E257-66.
78. Macleod DB, Habib AS, Ikeda K, Spyker DA, Cassella JV, Ho KY, *et al*. Inhaled fentanyl aerosol in healthy volunteers: Pharmacokinetics and pharmacodynamics. Anesth Analg 2012;115:1071-7.
79. Constant I, Nghe MC, Boudet L, Berniere J, Schrayer S, Seeman R, *et al*. Reflex pupillary dilatation in response to skin incision and alfentanil in children anaesthetized with sevoflurane: A more sensitive measure of noxious stimulation than the commonly used variables. Br J Anaesth 2006;96:614-9.
80. Candotti CT, Loss JF, La Torre M, Melo MO, Araújo LD, Marcks VV. Use of electromyography to assess pain in the upper trapezius and lower back muscles within a fatigue protocol. Braz J Phys Ther 2009;13:144-51.
81. Gruss S, Geiger M, Werner P, Wilhelm O, Traue HC, Al-Hamadi A, *et al*. Multi-modal signals for analyzing pain responses to thermal and electrical stimuli. J Vis Exp 2019;146:e59057.
82. Candotti CT, Loss JF, Pressi AM, de Souza Castro FA, La Torre M, de Oliveira Melo M, *et al*. Electromyography for assessment of pain in low back muscles. Phys Ther 2008;88:1061-7.
83. Ambroz C, Scott A, Ambroz A, Talbott EO. Chronic low back pain assessment using surface electromyography. J Occup Environ Med 2000;42:660-9.
84. Mieronkoski R, Syrjälä E, Jiang M, Rahmani A, Pahikkala T, Liljeberg P, *et al*. Developing a pain intensity prediction model using facial expression: A feasibility study with electromyography. PLoS One 2020;15:e0235545.

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