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Cerebral oxygenation for pain monitoring in adults is ineffective: A sequence-randomized, sham controlled study in volunteers☆

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HIGHLIGHTS

- Due to an increase of cerebral blood flow $SctO_2$ changes might quantify pain.
- In awake volunteers, frontal changes in $SctO_2$ via NIRS are most likely unspecific for pain.
- Point-of-care pain monitoring remains a challenge in adults.

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ABSTRACT

Background: Pain assessment by Numeric Rating Scale (NRS) is considered to be good clinical practice, but objective pain assessment is still a challenge. Near infrared spectroscopy (NIRS) measures cerebral tissue oxygen saturation ($SctO_2$) that increases with cortical-neuronal activity and may provide point-of-care bedside pain monitoring. Analogous to promising studies in newborns, we hypothesize that different levels of $SctO_2$ can probably quantify pain intensity. $SctO_2$ may increase following painful in contrast to non-painful or sham stimuli and may correlate with pain intensity as assessed by NRS in volunteers.
Methods: Twenty healthy male students (24.2 ± 1.9 years), recruited via local advertising, were consecutively included in a sequence-randomized, sham-controlled, single-blinded study. $SctO_2$ was recorded continuously with two NIRS sensors on the forehead. After resting, four stimuli were applied in a random order on the right forearm (unexpected and expected electrical pain, expected non-painful and sham stimuli). Blinded subjects were asked to rate each stimulus on NRS. Statistics: RM-ANOVA; Wilcoxon or paired Student *t*-test; Spearman's rank correlation; $P < .05$.
Results: Resting volunteers showed $SctO_2$ of 72.65% ± 3.39. $SctO_2$ significantly increased for about 60 to 70s until a maximum after unexpected painful (74.62% ± 3.9; $P = .022$) and sham stimuli (74.07% ± 3.23; $P = .014$). Expected painful ($P = .139$) and non-painful stimuli ($P = .455$) resulted in no changes in $SctO_2$. NRS scores (median, IQR) were rated significantly higher after expected (5.25, 3.5 to 6.75) than after unexpected (4.5, 3 to 5; $P = .008$) pain. No strong correlation was found between NRS and $SctO_2$.
Conclusions and Implications: Contrary to our expectations, measuring $SctO_2$ via a two-channel NIRS is not able to remediate the lack of objective bedside pain assessment under standardized experimental conditions in alert adults.
Trial Registration: DRKS 00011575 (retrospectively registered).

1. Introduction

Point-of-care diagnostics are at the focus of research for many years. Pain intensity assessment by Numeric Rating Scale (NRS) is considered to be good clinical practice, but objective assessment remains still a challenge, because bedside pain monitoring is still lacking.

For example, only conscious patients can score their pain on one-dimensional scales, such as the NRS. Pain ratings via scales are

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more or less subjective and not directly comparable between individuals. Vegetative signs like sweating or tears, heart rate (HR) or blood pressure (BP) are not sensitive and are non-specific for their use under clinical conditions. [1] Additionally, various parameters such as heartbeat intervals, heart rate variability, plethysmographic pulse wave amplitude, surgical stress index, skin conductance, pupillary dilatation reflex and electroencephalographic measures have been investigated, with controversial results. [2–8]

Cortical haemodynamic response may be an alternative and more central related measure of pain processing compared to behavioural or physiological measures. Cerebral oximetry, based on near infrared spectroscopy technology (NIRS), measures local concentrations of oxy-(HbO_2) and deoxy-haemoglobin (Hb) and provides regional cerebral tissue oxygen saturation ($SctO_2$) that increases with cortical-neuronal activity [9–11]. A two-channel NIRS is a widely used, non-invasive device [12] that can be used, for example, to reduce adverse clinical outcomes during cardiovascular surgery [13,14].

Promising studies of newborns have reported changes in somatosensory and frontal cortex activation, particularly in cerebral oxygenation measured by NIRS as a result of altered haemodynamic activity, after nociceptive procedures [15–19]. Additionally, functional NIRS (fNIRS) could differentiate signal changes of both innocuous and noxious stimuli in the primary somatosensory cortex contralateral to the stimulus in healthy subjects [20]. In sedated patients scheduled for heart surgery, increased $SctO_2$ values in the frontal cortex were observed during low nociceptive procedures [21]. Furthermore, in a pilot study of alert humans, a pain- and itch-related activation pattern of $SctO_2$ in the prefrontal cortex was determined using a multichannel-topography [22].

To our knowledge, cerebral oxygenation using a portable two-channel NIRS for bedside pain monitoring has never been investigated in alert adults under standardized, sham-controlled conditions. We hypothesize that different levels of $SctO_2$ can probably quantify pain intensity. Therefore, we designed a randomized, placebo-controlled study exposing alert volunteers to experimental painful, non-painful and sham stimuli. We postulate that $SctO_2$ increases following painful stimuli in contrast to non-painful and sham stimuli and that it correlates with stimulus intensities and pain ratings via NRS in volunteers.

2. Materials and methods

This single-blinded, sequence-randomized cross-over study was conducted with volunteers upon receiving written consent. The study protocol was approved by the local Ethics Committee of the Faculty of Medicine of the Ruhr University Bochum, Germany (Chairman: Prof. Dr. M. Zenz; Gesundheitscampus 33, 44801 Bochum, Germany; No. 4501-12; date of approval: 23 Oct 2012). The experimental procedure was in accordance with the Declaration of Helsinki and the manuscript adheres to the applicable Equator guidelines.

2.1. Subjects

The study recruited male subjects (mean age 24.2 ± 1.9 years) via local advertising starting on 2 January 2013. All 20 consecutively included participants were right handed and healthy. Volunteers with any anamnestic disorders or who had received medical consultation in the previous six months and those who were taking regular medication or who had exposure to medications for analgesia in the previous three months were excluded. Subjects were not aware of the study hypothesis.

2.2. Cerebral oximetry

Cerebral oximetry by means of near infrared spectroscopy provides information on the availability of oxygen in brain tissue [23]. It measures continuous local concentrations of oxy- and de-oxygenated haemoglobin and regional cerebral tissue oxygen saturation ($SctO_2$) at the microvascular level [24]. Usually, it presents a mixed oxygen saturation and reflects a proportional mix of arterial (~30%) and venous (~70%) blood in the outlying regions of the brain [25]. $SctO_2$ is defined as a ratio of oxygenated haemoglobin and total haemoglobin (HbT) concentrations in brain tissue ($SctO_2 = 100\% \times HbO_2/(Hb + HbO_2)$). It non-invasively reflects regional cerebral metabolism and the balance of local cerebral oxygen supply and demand. Near infrared light (absorption spectra 770 to 910 nm) from a FORE-SIGHT™ Cerebral Oximeter (MC-2030, CAS Medical Systems, Inc., Branford, U.S.A.) penetrates the brain to measure mostly grey matter in the frontal cortex region [26], and absolute values are updated every 2 s (s) on the monitor (ratio arterial to venous blood 70/30). Displayed in a range from 0 to 99% are $SctO_2$ levels for the right (R-$SctO_2$) and left (L-$SctO_2$) hemispheres and averaged for both as $SctO_2$ in general. $SctO_2$ increases with cortical-neuronal activity due to cerebral vasodilatation with an increase in cerebral blood volume [9–11,26] or decreases, for example, due to oxygen deficiency.

2.3. Study design

All volunteers, participating in a single session, lay on their backs in a darkened and silent laboratory and were asked to shut their eyes. All subjects were told that four painful stimuli would be applied after a warning and that they would rate the pain level after each stimulus between 0 and 10 (0 = no pain, 10 = most intense pain imaginable) on NRS. The use of decimal scores was permitted.

Two standard single-use NIRS sensors were placed on the right and left sides of the adult forehead after skin defatting. A self-made electrode consisting of 12 pins was fixed 5 cm distal to the crook of the right ventral arm. A painful electrical stimulus of 2 mA was administered there for 5 s at 100 Hz with a constant-current stimulator (DS7A, Digitimer, Welwyn Garden City, UK). [8]

The session started with a baseline measurement for 5 min without any disturbance to adjust to the situation (pre-Base 1). Next, four different stimuli were successively applied. See Fig. 1. For each subject, the first stimulus was an electrical unexpected painful stimulus (UPS) that was against the expectation given without warning. The next stimulus was an electrical expected painful stimulus (EPS) or a neutral non-painful stimulus (NPS) or a placebo stimulus (PS). All subsequent stimuli were given in a previously generated computer-based random order (six different order options) at '0s', each following a repeated announcement, within a latency time of 30 s. EPS was set with identical intensity to UPS, but was announced beforehand. Except the unexpected first stimulus, all stimuli were preceded by a warning and expected to be painful due to the instruction given at the beginning. The NPS consisted of a spray of disinfectant on the right ventral forearm and after announcement of placebo stimulus, no stimulus was given at all. Between two stimuli, there was a resting phase of 5 min: 0 to 150 s recovery time, followed by a new baseline for 150 s for the next stimulus. All data were analyzed offline.

2.4. Data and statistical analysis

The FORE-SIGHT™ Cerebral Oximeter recorded an averaged $SctO_2$, R-$SctO_2$ and L-$SctO_2$ every 2 s. Our data revealed consistently higher values for R-$SctO_2$ than for L-$SctO_2$. To simplify, we therefore reported the bifrontal $SctO_2$ of predetermined observational time intervals. Each stimulus (UPS, EPS, NPS or PS) was set at '0 s' and