PERIOPERATIVE PAIN ASSESSMENT AND MANAGEMENT

Objective monitoring of nociception: a review of current commercial solutions

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Summary

Nociception, in contrast to pain, is not a subjective feeling, but the physiological encoding and processing of nociceptive stimuli. However, monitoring nociception remains a challenge in attempts to lower the incidence of acute postoperative pain and the move towards a more automated approach to analgesia and anaesthesia. To date, several commercialised devices promise a more accurate reflection of nociception than the traditionally used vital signs, blood pressure and heart rate. This narrative review presents an overview of existing technologies and commercially available devices, and offers a perspective for future research. Although firm conclusions about individual methods may be premature, none currently appears to offer a sufficiently broad applicability. Furthermore, there is currently no firm evidence for any clinically relevant influence of such devices on patient outcome. However, the available monitors have significantly aided the understanding of underlying mechanisms and identification of potential pitfalls.

Keywords: analgesia; nociception; nociception index; nociceptive flexion reflex; pupillometry; skin conductance; surgical pleth index

The International Association for the Study of Pain (IASP) defines *pain* as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage'.[1] The freedom of pain has long been defined as a basic human right. Research activity in this field is not surprisingly high, and the knowledge about the pathophysiology and treatment of acute pain is ever increasing. However, the incidence of moderate-to-severe acute postoperative pain has not changed for several decades, and is still reported to be somewhere between 20% and 80%.[2,3] Problematically, pain is, by its very nature, subjective, *per se* non-existent, and hence, unmeasurable in anaesthetised subjects. What can be monitored is nociception or the (patho-)physiological

response to it. Nociception, in contrast to pain, is not a subjective feeling, but the physiological encoding and processing of nociceptive stimuli. Both pain and nociception may exist without each other.[4] This review will use the term 'nociception' monitoring from here on.

When investigating the idea of monitoring nociception, it is worth to consider that the freedom of intraoperative nociception is by far less uncontroversially discussed than the freedom of (conscious) pain. The proponents of opioid-free anaesthesia may well argue that only the control of nociception-provoked symptoms (i.e. haemodynamic effects), but not abolishing nociception *per se*, is ultimately relevant.[5] Nociception by itself is also very difficult, if not impossible, to measure in the clinical environment. This poses a

significant hindrance to the reliable validation of respective monitors.

However, monitoring nociception remains an important goal. It may allow decreasing intraoperative stress response beyond simply controlling haemodynamics. Nociception monitors could be integrated into closed-loop systems for the administration of analgesics, and identification of patients with a higher likelihood for severe postoperative pain may allow more targeted pre-emptive analgesia. Such a technology could be of significant benefit in settings, such as the ICU, where communication between patient and caregiver is frequently impaired, but pain/nociception is extremely prevalent.

This narrative review is based on a literature search in the PubMed National Library. The main search terms were 'nociception', 'surgical pleth index', 'analgesia nociception index', 'nociception level index', 'skin conductance', 'pupillometry', 'nociceptive flexion reflex', and 'Qnox'. Only references with at least an abstract published in English were considered. No publication was deliberately omitted to bias the outcome of this review. However, the author has taken the liberty of not quoting papers that neither aid the understanding nor advance the knowledge about a specific method. Although comprehensive, the review does not claim to discuss all possible ideas of nociception monitoring, but aims to focus on concepts with commercial solutions.

Monitoring principles and limitations

As the quantification of nociception in unconscious subjects is extremely difficult, it is the 'reaction' to nociception that is being used for the purpose of monitoring. The most frequently utilised response to 'surgical stress' is an increase in sympathetic activity or the corresponding decrease in parasympathetic tone.[6] This, of course, assumes that nociception will trigger a shift in the sympatho-vagal balance towards a sympathetic stress response. Changes in cardiac autonomic control (i.e. increased HR), increased peripheral vasoconstriction, pupillary dilatation, and an increase in galvanic skin conductance offer a relatively easy access to the evaluation of such sympathetic response. Overall, these changes describe common observations in stressed humans: a fast HR, dilated pupils, and cold and sweaty hands. In addition to these 'simple' reactions, stress may also influence the HR variability (HRV),[7] electroencephalographic and electromyographic patterns,[8] and the threshold of peripheral reflexes[9]—obviously, more subtle changes usually hidden from simple observation.

The most commercially available monitors are based on the detection of one (Analgesia Nociception Index [ANI], Skin Conductance, pupillometry, and nociceptive flexion reflex [NFR] threshold) or two (surgical pleth index [SPI] and qNOX) of the aforementioned parameters. The only multi-parameter approach may currently be the nociception level (NOL) index.[10] However, whether one, two, or multiple parameters offer the optimum solution for monitoring nociception is not yet known. Table 1 offers an overview over the existing commercialized monitoring solutions.

Limitations

All the aforementioned approaches have significant limitations. Although less relevant in unconscious subjects, arousal and emotions are obvious and strong confounding factors on the sympatho-vagal balance.[11] This may explain why the sympathetic stress response to acute postoperative pain has been reported to be much less linear and much more unpredictable than suggested by textbook knowledge.[12] The cardiovascular autonomic control is also influenced by a plethora of medications and intraoperatively used drugs, such as beta-receptor blockers, vasoactive drugs, or atropine.[13] The presence of a pacemaker and cardiac arrhythmia are further confounders.[13] Changes in intravascular fluid status, such as a fluid challenge, are also known to affect some scores.[14] In addition, the accuracy of nociception scores is likely influenced by the type of general anaesthesia, as significant differences in the stress response during volatile vs total i.v. anaesthesia have been described.[15] As autonomic tone changes from birth to senior age, patient age is yet another confounding factor.[16] The assessment of the pupillary diameter may be hindered by the miotic effects of opioids, and neuromuscular blocking drugs may hinder the monitoring of electromyographic changes in scores, such as qNOX.[8] Although methods, such as the nociception flexion reflex (NFR) threshold, may be less prone to the confounding effects of perioperative medication (neuromuscular blocking agents possibly exempted), the more awkward set-up and limited access to the patient's leg may still pose a significant hindrance to its routine use.

Yet, against all aforementioned odds, several solutions for nociception monitoring have been (successfully) commercialised and are described in the following sections.

Single-parameter scores

Analgesia nociception index (ANI, Mdoloris Medical Systems, Loos, France)

Analgesia Nociception Index is a dimensionless score (0−100) based on the analysis of the area under the curve of the high-frequency spectrum of the HRV. The manufacturer claims that higher ANI scores reflect higher parasympathetic activity,[17] and hence, a state of lower stress response and possibly less nociception. ANI also aims to account for the effects of the respiration rate, which has a significant confounding influence on the individual parameters of the HRV.[18] ANI has been investigated in both conscious and anaesthetised subjects. In awake patients, Boselli and colleagues[19] reported an association between acute postoperative pain and ANI scores, with very high negative predictive values (NPVs; 88%) of higher ANI scores (>57) for the exclusion of significant (>3/10) acute pain. However, this study investigated patients with a relatively low incidence of postoperative pain. The high NPV may therefore be at least in part attributable to a statistical artefact. Several subsequent studies found no clinically relevant association between ANI and acute postoperative pain.[20−22] A further study in awake volunteers subjected to sham and noxious stimuli concluded that ANI did not allow a differentiation between sham vs noxious stimuli, and that ANI was likely significantly influenced by emotions.[23] Although a study investigating the association between an established paediatric pain scale (The Face, Legs, Activity, Cry, Consolability scale) and ANI showed higher ANI scores in children after surgery vs children without surgery,[24] the actual clinical value of this study remains unclear. Boselli and colleagues[25] reported that ANI was increased in hypnotised vs fully conscious healthy adult volunteers. Although this is of little direct clinical relevance, it may at least be a useful 'proof of concept' showing that a more relaxed state is associated with higher ANI scores. A study conducted in patients on the ICU found

Table 1 Overview of pain and nociception monitors.

	Device	Score/unit	Measurement principle	Monitoring nociception	Monitoring pain	Comments
Single-parameter scores	Analgesia nociception index	0—100; dimensionless	Cardiac parasympathetic tone	Possibly negative predictive value (ANI <43 at end of surgery) for absence of significant postoperative pain[33]; value for pre-emption of haemodynamic events controversially discussed[29,30]; may 'react' to noxious stimuli somewhat stronger than standard haemodynamics, but controversial[17,27,28]	Possibly some negative predictive value for exclusion of significant pain, but controversially discussed[19—22,26]	Well published; may be best for exclusion of significant nociception/pain
	Skin conductance	Number of fluctuations in skin conductance per second (NFSC) (n)	Peripheral (skin) sympathetic tone	NFSC >0.2 may correlate with severe nociception and, at the end of surgery, significant postoperative pain[7,37]	Influence by many confounders (i.e. arousal) may limit its use in awake patients[37—40]	Easy to use, but NFSC tends to react predominantly with higher levels of stress/nociception ('smoke detector')
	Pupillometry	Absolute or changes in pupillar width (mm %$^{-1}$)	Sympathetic tone (pupillar innervation)	Pupillometry-guided analgesia may reduce opioid consumption and persistent pain (but only n=55 included subjects)[44]; may predict responsiveness to postoperative opioids[43]; influenced by depth of anaesthesia[52]	May predict response to noxious stimulus in the ICU[50]	Promising results, but somewhat awkward method (requiring repeated access to open eye)
	Nociceptive flexion reflex threshold	mA	RIII reflex modification by level of analgesia	May aid the prediction of a response to a noxious stimulus[54]; limited predictive value for postoperative pain when measured at the end of surgery[9]	Little published research in the postoperative setting	NFTS is a reasonably well-known instrument in pain research, but its perioperative use in clinical routine is not yet well researched
Two-parameter scores	Surgical pleth index (SPI)	0—100; dimensionless	Peripheral vascular and cardiac sympathetic tone	Meta-analysis (six publications and 463 patients) states that SPI-guided analgesia resulted in lower opioid consumption and shorter times to tracheal extubation[61]; conflicting evidence regarding the prediction of acute postoperative pain[57,63]; 'ideal' score during surgery may be affected by age and might be closer to 30 (vs frequently quoted <50)[57,62]	Manufacturer does not recommend use in conscious patients; little or no use in awake subjects[7]	Well researched, but guidelines for ideal range of SPI overall not well validated; only monitor which does not require consumables (but GE monitor)
	qNOX	0—99; dimensionless	Electromyographic/ electroencephalographic patterns associated with nociception	May help to predict probability of sudden movement in response to stimulation[8]	No published data to evaluate the score in this setting	To date, insufficient evidence to allow firm conclusions about perioperative use and its benefits

Continued

Table 1 Continued

Device		Score/unit	Measurement principle	Monitoring nociception	Monitoring pain	Comments
Multi-parameter scores	Nociception level (NOL) index	0–100; dimensionless	Four parameters: skin galvanic response (sympathetic tone), plethysmographic pulse wave (sympathetic vascular tone), temperature, and accelerometry (association with nociception unclear)	May discriminate noxious stimuli slightly better than standard haemodynamics[65,67]; 'ideal' intraoperative NOL may be 10–25[10]	No published data	Multiple parameters may increase accuracy, but, to date, little evidence for clinical relevance

only weak associations between noxious stimuli and changes in the ANI score, and concluded that ANI had 'only weak psychometric properties to detect pain'.[26] However, the same study did report a strong NPV of ANI (>43) for the absence of significant pain. ANI may therefore not be suitable for the use in awake or only mildly sedated patients. Several studies have compared ANI with other vital signs/monitors for the assessment of nociception in anaesthetised patients.[17,27] However, although some studies found ANI to be of slightly higher 'reactivity' to noxious stimuli, others concluded that ANI was 'at least as good as blood pressure and heart rate', a statement ultimately discounting any real benefit of the score.[28] The manufacturer of the ANI monitor claims that the score may predict undesirable intraoperative haemodynamic changes, hence aiding their prevention. An evaluation of the predictive value of ANI for haemodynamic changes during surgery has resulted in conflicting reports, with one group reporting the sensitivity/specificity of the score as high (88% and 83%, respectively, for ANI <55 to predict haemodynamic changes within 5 min),[29] whilst the other as low (predictive probability of ANI to detect changes (>10% from baseline) in HR=0.61 and in BP 0.59 (0.5=tossing a coin).[30]

In children anaesthetised with sevoflurane/remifentanil, ANI showed a weak association with intraoperative noxious stimuli, and the authors concluded ANI to be of some clinical value. However, the percentages of children whose ANI remained in the 'inconclusive zone' (predicting neither presence nor absence of a noxious stimulus) were 41%, 51%, and 33% for ANIi, ANIm, and DeltaANI, respectively.[31] A second study evaluating the score in the setting of paediatric anaesthesia found that ANI correlated better with a perceived (attending anaesthetist) lack of analgesia and the re-establishment of sufficient analgesia than HR.[32]

In an investigation of the predictive value of ANI monitoring at the end of surgery, Boselli and colleagues[33] found that an ANI >50 had a high (92% for ANI >50) NPV for moderate-to-severe postoperative pain. However, to date, this study remains the only associated publication, and prospective validation of these results is required. ANI-guided intraoperative analgesia has been reported in several publications with overall inconclusive results. Although ANI-guided analgesia may slightly reduce intraoperative opioid consumption,[34] it failed to result in a significant reduction of opioid-related side-effects.[35,36]

Summary

Analgesia Nociception Index is a 0–100 dimensionless score, which is calculated from the assessment of the HRV. Higher ANI values are thought to represent higher parasympathetic activity and possibly less pain/nociception. Studies about the use of ANI to predict intraoperative haemodynamic changes and about the ANI monitoring of intraoperative nociception are overall inconclusive. In (semi-) conscious patients, ANI appears to be influenced by emotions and other confounders. However, ANI (≥50) has shown a high NPV for the absence of acute postoperative pain and pain in the ICU. To date, no evidence exists for a clinically relevant benefit of ANI monitoring.

Skin conductance (MedStorm innovations, AS, Oslo, Norway)

The assessment of electrical skin conductance is a long-known tool for the quantification of stress (i.e. in a lie

detector application), and may represent an additional 'vital sign' rather than an actual pain score. With the filling of palmar and plantar sweat glands under sympathetic control, micro-fluctuations in skin conductance caused by rapid changes in the water permeability of the excreting ducts appear to allow an easily accessible insight into rapid changes of sympathetic tone. The parameter of the number of skin conductance fluctuations per second (NFSC) aims to reflect the rate of such 'sympathetic chatter'. Skin conductance monitors usually apply a micro-current to the palmar surface of the hand (adults) or plantar surface of the feet (i.e. neonates), and measure the conductance of such current between two electrodes.

An NFSC >0.2 may correlate with severe postoperative pain and possibly also intraoperative nociception.[7,37] However, NFSC did not reflect the increase in anti-nociception caused by the intraoperative administration of fentanyl.[37]

The confounding effects of arousal (or too light anaesthesia) and postoperative confounders (i.e. noise levels and anxiety) have largely hindered its clinical use for the assessment of postoperative pain or intraoperative nociception.[37–39] In children, skin conductance only correlated poorly with conventionally assessed pain levels.[38,40] In contrast, skin conductance was significantly increased after a heel prick test in neonates.[41] However, the clinical value of a monitor indicating pain as a result of a clearly painful stimulus is questionable.

Interestingly, the concept of skin conductance monitoring has been most recently implemented into the multi-parameter NOL index.

Summary

The assessment of skin conductance (lie detector principle) allows the identification of time points with higher sympathetic activity. The number of micro-fluctuations in skin conductance per second may, in this context, be a more sensitive indicator for stress. However, many confounders influence skin conductance in awake subjects. During anaesthesia, skin conductance appears to be a relatively crude measurement for nociception and may be more useful as a 'smoke detector' in case of significant intraoperative stress response. There is currently no evidence for a clinically relevant benefit arising from the perioperative utilisation of skin conductance monitoring.

Pupillometric assessment of nociception (i.e. AlgiScan; IDMed, Marseille, France)

The pupillary diameter and its variations are significantly influenced by the sympatho-vagal balance.

The assessment of pupillary diameter, its variation, and its unrest in ambient light have been examined for the prediction of pain,[42,43] intraoperative monitoring of nociception,[44–47] and postoperative pain in PACU[48,49] and pain in the ICU.[50,51]

Neice and colleagues[43] found that the responsiveness to postoperative opioid treatment could be predicted from the degree of pupillary unrest in ambient light. Low levels of unrest before opioid analgesia were associated with a lower responsiveness to opioid treatment. Guiding intraoperative remifentanil administration, Sabourdin and colleagues[44] found lower opioid consumption in PACU, but also lower levels of persistent pain 3 months after the operation in 55 patients randomised into either standard or pupillometry-

guided analgesia. In this context, it is interesting to note that the assessment of postoperative pain by the same means appears to be hindered by the lasting effects of intraoperative opioid treatment and its effect on the pupillary diameter.[48,49] Intraoperative pupillometric assessment was also influenced by the depth of anaesthesia, not just the level of anti-nociception.[52] In the ICU, the pupillary response to standardised noxious stimuli (i.e. 20 mA tetanic nerve stimulation) predicted a reaction to tracheal suctioning.[50] Wildemeersch and colleagues[51] described the relatively easy implementation of the method in an ICU, but also concluded that further scientific evaluation was required.

Summary

Pupillometric monitoring of nociception has shown some promising results, such as a reduction in persistent postoperative pain. However, the method is influenced by several significant confounders (i.e. opioids), and all studies available to date are relatively small. Hence, there is a high risk of such investigations being under-powered for endpoints with a relatively low event rate (i.e. the prevalence of persistent pain). Although the method appears more complex to use, an implementation in the ICU has been reported. At present, no firm conclusions can be drawn about the clinical value of pupillometric nociception monitoring because of a lack of larger-scale RCTs.

NFR threshold (NFTS Paintracker; Dolosys, Berlin, Germany)

The threshold of the NFR (also known as RIII reflex) can be monitored (i.e. at the leg). The NFR is a polysynaptic spinal withdrawal reflex that is elicited after the activation of nociceptive A delta afferents. To quantify the reflex threshold, the electromyographic activity of the biceps femoris muscle is monitored during the application of varying intensities of electrical stimulation to the ipsilateral sural nerve. Based on the observed response, the intensity of stimulation required to elicit the NFR is used to define the nociceptive threshold.[53] This threshold may increase with increased levels of analgesia, and has been found to be able to predict sudden movement as a result of a noxious stimulus.[54] However, although in this study by Jakuscheit and colleagues,[54] NFTS had some predictive probability (0.63 [95% confidence interval {CI}: 0.59–0.67]); this was relatively low (predictive probability of 0.5=tossing a coin) and lower than that of the bispectral index. Measured at the end of surgery, just before tracheal extubation, the NFTS also showed some limited predictive value for postoperative pain in PACU.[9] A study by Rhudy and colleagues[55] investigating the effect of placebo treatment of pain concluded that this had a significant effect on the nociception threshold reflex. Jurth and colleagues[56] recently published a new model for NFTS calculation, which promises an increased precision of the NFTS estimation. However, this has not yet been further investigated.

Summary

The threshold of the NFR differs methodologically from other monitoring solutions for the assessment of nociception. Its relative independence from various confounders influencing the sympatho-vagal balance may be a significant benefit, but this may be outweighed by the more complex set-up and the

limitations arising from problems with accessing a patient's leg during surgery. However, studies investigating the method in the perioperative context are extremely limited and generally small. It is hence too early to judge the value of NFTS for everyday clinical use.

Two-parameter scores

Surgical pleth index (GE Healthcare, Helsinki, Finland)

This GE proprietary score is sought to be calculated from the pulse-wave amplitude and the heartbeat interval. The published equation for the score is $SPI=100-(0.7\times PPGAnorm+0.3\times HBInorm)$, in which PPGAnorm is the normalised plethysmographic pulse-wave amplitude, and HBInorm is the normalised heartbeat interval. Overall, SPI appears to represent a combined assessment of peripheral (sympathetically mediated) vasoconstriction and cardiac autonomic tone. Different from most other commercial devices, SPI does not use any consumables, as all required data are generated via the (GE proprietary) S_pO_2 finger probe.

The GE-recommended range for intraoperative SPI is <50 (0–100 score), with lower values probably indicating less stress response/nociception. For intraoperative patients, most studies have used an SPI range of 20–50 to describe an acceptable level of analgesia. Postoperative arousal has a significant effect on SPI, rendering the score useless during this period of time.[57] In conscious subjects, SPI has found to be of no value for the assessment of pain in the recovery room.[7] Consequently, using SPI in conscious subjects is not recommended by the manufacturer. Intraoperatively, SPI does appear to reflect certain intraoperative stimuli, but it remains questionable whether this constitutes an actual clinical benefit.[37] In a setting of total i.v. anaesthesia, SPI-guided analgesia resulted in lower propofol consumption and faster awakening.[58] However, this could not be replicated in patients receiving volatile-based anaesthesia.[59] In children, SPI-guided analgesia resulted in more postoperative agitation and higher opioid requirements when compared with standard practice.[60] It is therefore surprising that a recent meta-analysis of SPI-guided analgesia by Won and colleagues[61] concluded that SPI guidance resulted in a significantly lower opioid consumption and shorter times to tracheal extubation when analysing six randomised controlled studies including 463 patients. However, the high heterogeneity (i.e. anaesthetic technique) and the small number of included papers may hinder firm conclusions to be drawn from this study. A recent publication in multi-trauma patients found that both vasopressor consumption and opioid requirements were lower after a combination of entropy and SPI guidance of anaesthesia vs standard care.[68] However, it remains unclear whether the guidance by entropy or by SPI was dominantly responsible for the observed benefits. As mentioned earlier, SPI values of 20–50 are usually utilised to describe an acceptable range for intraoperative analgesia. However, the evidence for this recommendation is relatively sparse. Two studies have postulated that the 'ideal' SPI may be significantly influenced by age (children vs adults),[62] and that it could be possibly lower (i.e. at or below 30).[57] The use of a different, possibly lower, value for SPI to define the maximum score still representing sufficient analgesia may hence potentially improve SPI-guided anaesthesia. Although SPI has been suggested to have some value for the prediction of acute postoperative pain (positive predictive value [PPV] 89.7 for SPI >30 indicating pain >3/10),[57] a more

recent study testing the SPI cut-off value of 30 for the prediction of moderate-to-severe pain prospectively in 200 patients has essentially refuted this (PPV for SPI >30 to predict pain >3/10 only 60%).[63]

Summary

Surgical pleth index is a dimensionless 0–100 score based on the assessment of peripheral and cardiac autonomic tone. The method is unique in so far that it does not require any additional consumables, but the use of a GE anaesthesia monitor. SPI has been widely studied perioperatively and is not considered useful in awake subjects. SPI-guided anaesthesia has been found to result in lower opioid consumption and short times to patient arousal in a recent (small) meta-analysis. However, other investigations have reported contradictory results, and the clinical relevance of the described benefits remains to be further examined.

qNOX (qCON 2000 Monitor; Quantium Medical [Fresenius Kabi], Mataró, Spain)

The qCON monitor displays two separate scores: qCON to reflect the depth of anaesthesia and qNOX claiming to reflect the depth of analgesia. qCON has been shown to correlate relatively well with other measures of anaesthetic depth, such as the bispectral index.[8]

The qNOX score (0–99) is an EEG- and EMG-based dimensionless proprietary score. The mathematical model used for the development of qNOX is an adaptive neuro fuzzy inference system, which has been described in more detail in an early validation study for the score by Jensen and colleagues.[8]

qNOX appears to aim to reflect the likelihood of a (movement) response to a noxious stimulus. According to the manufacturer, a qNOX <40 signifies a very low likelihood, 40–60 a low likelihood, and >60 a higher likelihood of a response to a noxious stimulus (http://quantiummedical.com/products/qcon2000/). In a setting of total i.v. anaesthesia, the reactions of 60 patients to noxious stimuli were evaluated. The qNOX pre-stimulus values were significantly different (P<0.05) for movers vs non-movers as a response to laryngeal mask airway insertion (62.5 [24.0] vs 45.5 [24.1]), tracheal intubation (58.7 [21.8] vs 41.4 [20.9]), and laryngoscopy (54.1 [21.4] vs 41.0 [20.8]). There were no significant differences in remifentanil or propofol effect-site concentrations for movers vs non-movers.[8] A second study investigating 140 patients mainly found that qNOX and qCON (proposed to reflect the level of consciousness) scores were not identical and responded to different stimuli/at different time points, possibly reflecting the two independent dimensions, anaesthesia and analgesia.[64]

Overall qNOX represents an interesting alternative to most other monitors for the assessment of nociception, as it does not rely on a measure of (peripheral) autonomic activity. This may render the score more robust against the influence of cardiovascular medications and co-morbidities. However, the inventors caution that neuromuscular blocking agents were likely to distort the score because of its use of EMG signals.[8]

Summary

qNOX is an EEG-/EMG-based score (0–99) claiming to represent the increasing likelihood of a response to a noxious stimulus with increasing qNOX score values. Although the independence from many potential confounders affecting other

nociception monitors (i.e. vasoactive drugs) makes the concept appealing, there is currently insufficient evidence to draw any firm conclusions about the clinical use of the score.

Multi-parameter scores

NOL index (Medasense, Ramat Gan, Israel)

To date, NOL may be the only commercially available true multi-parameter nociception/pain score. Like ANI and SPI, it is a dimensionless score of 0–100, calculated via a proprietary algorithm and based on four sensors (photoplethysmography, galvanic skin response, temperature, and accelerometer). All sensors are implemented into a finger clip, similar to a peripheral oxygen saturation monitor, and hence, similarly easy to use. Being a proprietary score, it is unclear whether and how the temperature and accelerometric data are used for the calculation of the score, as early publications have not mentioned it.[10] Used to detect intraoperative noxious stimuli under total i.v. anaesthesia, NOL has been found to be more 'reactive' than HR or MAP. Remifentanil *per se*, without stimulation, had no effect on NOL, but lowered both HR and MAP.[10] Martini and colleagues[10] suggested a NOL of 10–25 as being most appropriate for the maintenance of analgesia during general anaesthesia. A second study confirmed the stronger reaction of NOL (*vs* HR and MAP) to intraoperative noxious stimuli.[65] In another trial, NOL-monitored patients did either receive epidural analgesia or not. The reaction to a skin incision was more pronounced in the non-epidural group: NOL increased by 13.9 points (CI: 7.4–20.3; $P=0.0001$), compared with 5.4 points (CI: −6.3 to 17.1; $P=0.29$) in patients with epidural analgesia.[66] In a setting of desflurane–remifentanil anaesthesia, NOL was compared with standard vital signs and to ANI. NOL, but also all other parameters, responded to intraoperative noxious stimuli, with NOL and ANI 'performing' slightly better than the standard vital signs.[67]

Summary

NOL is a 0–100 multi-parameter score derived from a single finger-clip sensor. During general anaesthesia, NOL may best be kept around 10–25. At present, no research exists for the use of NOL in conscious subjects or patients in the ICU. Although NOL has been found to react more pronouncedly to noxious stimuli when compared with standard vital signs, it is unclear whether this alone represents a clinically relevant benefit. The current lack of fully independent (neither Medasense employees nor researchers being named to be on the company's advisory board) studies does not allow a firm statement about the clinical use for NOL.

Discussion and future directions

Despite many studies reporting statistically significant 'benefits' for the use of nociception scores *vs* traditionally used vital signs, to date, none has proved these differences to be of actual clinical relevance. Many initially encouraging results were later replaced by more moderate or even negative findings. One of the main reasons for this phenomenon may be the publication of many small 'pilot' studies with no sample size calculation at all, or of trials under-powered to warrant their frequently over-enthusiastic conclusions. Future research in this area would hence significantly benefit from a more careful approach to sample size calculation and more cautious and realistic assumptions. Frequently, researchers have gone straight from the first published trial about a new methodology to studying 'method-guided' intraoperative analgesia. Plenty of in-between steps (i.e. validation of manufacturer guidelines about 'ideal' score values during anaesthesia) are still missing, and this may explain why 'score-guided' analgesia has yet to show convincing advantages. Many currently available nociception scores appear to be designed to achieve, frequently only vaguely defined, 'desirable' intraoperative values with the relative ease of a standard anaesthetic. To avoid scores appearing to be 'stuck in the middle' (a score that does not appear to reflect anything but the extremes of stress) throughout surgery, a redesign of many current scores would potentially aid a more meaningful quantification of nociception during the 'steady-state phase' of intraoperative anaesthesia. This may include changing linear to logarithmic scales, or leaving the (pseudo-)accuracy of 0–100 scales in favour of a more simplified 'traffic light scale' approach. Hypothetically, multi-parameter scores may be more robust against confounding factors. Hence, a combination of available measures of nociception assessing the matter from different angles (i.e. cardiac autonomic tone and electroencephalographic assessment) may offer desirable features. However, currently, there is no convincing evidence for the superiority of multi-parameter scores.

Conclusions

Monitoring of nociception is a relatively new science. However, with the over-arching goal of more automated anaesthesia in mind, monitoring analgesia has become increasingly desirable. Within the past decade, several monitoring solutions have been commercialised. The most available monitors represent single-to-two-parameter scores, with only one (NOL) attempting a multi-parameter approach. All, but one (qNOX), of these devices utilise the assessment of autonomic tone.

Although all devices appear to reflect intraoperative stimuli slightly better than traditionally used parameters, such as BP or HR, to date, none has shown a convincing and clinically relevant benefit for its routine use.

However, quantifying nociception/analgesia remains the 'Holy Grail' in anaesthesia monitoring, as it not only promises to reduce the incidence of severe postoperative pain significantly, but also the incidence of opioid-related side-effects.

Author's contribution

Conducted the literature review and wrote paper: TL.

Declaration of interest

The author has received travel grants, speaker fees, or honoraria for consultation from GE Healthcare, Mdoloris Medical Systems, MedStorm Innovations, and Philips. However, none of the aforementioned companies nor any other third party had an influence on this review.

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