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Mini Review

Pain Monitors Futile Utopia or Future Standard of Care? A Mini-Review

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Abstract

Objective: The aim of this narrative review was to look for evidence of benefits that can be added by introducing pain monitors in the clinical practice. Pain monitor was defined as any device or method applied to identify a nociceptive stimulus.

Methods: A search for clinical trials evaluating a pain monitor in humans was conducted in PubMed, CENTRAL and Scopus in December 2017 with the following key words: pain monitor.

Results and Discussion: The bispectral index (BIS) monitor has some value in identifying painful stimuli. CARDEAN-guided intraoperative opioid administration reduces the incidence of unpredictable movements in unparalysed adult patients. Unstimulated composite variability index depends more on hypnotic drugs than on opioid concentration. The qNox can predict unwanted movements in unparalysed asleep adults. Fascial electromyography allows to distinguish between the analgesic and the hypnotic components of general anaesthesia in adults. Entropy-guided drug administration decreases analgesia requirement in the postoperative care unit. Heart rate variability correlates with pain scores in adults. Analgesia/nociceptive (ANI) index -guided intraoperative opioid administration reduces postanaesthesia care unit pain scores and analgesic requirements. In the paediatric population, ANI reflects the nociceptive/analgesia balance and can identify failed regional blocks in asleep children. Nociceptive level can differentiate noxious from nonoxious stimulation in adults. Intraoperative pupillary reflex dilatation (PRD)-guided opioid administration reduces acute postoperative pain and early postoperative analgesic requirements in adults. In asleep children, PRD is more sensitive to noxious stimulation than heart rate, blood pressure and BIS. Skin conductance has been reported as being of moderate interest in adults and in children. Intraoperative surgical stress index (SSI)-guided opioid administration reduces opioid consumption and produces faster recovery in adults undergoing ambulatory or ear, nose and throat surgery. In children, SSI is not superior to haemodynamic parameters to identify painful stimulation.

Conclusion: It seems possible to identify a painful stimulation from a pain monitor. Various technologies have been studied. More randomized controlled trials comparing pain monitor-guided intraoperative drug administration with standard care are required before a cost/benefit ratio can be established.

Keywords: *Pain Monitor; Skin Conductance; Analgesia Nociception Index; Pupil Reflex; Surgical Stress; NOL Monitor; Perioperative Pain; Wavelet Transform; Bispectral Index Monitor; Entropy; Electroencephalogram*

Abbreviations

AAI: A-Line Autoregressive Index; ANI: Analgesia Nociceptive Index; BIS: Bispectral Index; CI: Confidence Interval; CPOT: Critical-Care Pain Observation Tool; CVI: Composite Variability Index; EEG: Electroencephalogram; EMG: Electromyography; ENT: Ear, Nose and Throat; EP: Evoked Potentials; FEMG: Facial Electromyography; FLACC: Face Legs Activity Cry Consolability Scale; GA: General Anaesthesia; HRV: Heart Rate Variability; MAC: Minimal Alveolar Concentration; NFSC: Number of Fluctuations in Skin Conductance; NFRT: Nociceptive Flexion Reflex Threshold; NSRI: Noxious Stimulation Response Index; PACU: Postanaesthesia Care Unit; PIPP: Premature Infant Pain Profile; PRD: Pupillary Reflex Dilatation; PLRA: Pupillary Light Reflex Amplitude; PWR: Pulse Wave Reflex; RA: Regional Anaesthesia; RCT: Randomized Controlled Trial; SVmR: Skin Vasomotor Reflex; SSI: Surgical Stress Index; VAS: Visual Verbal Analogical Pain Score; WTCRC: Wavelet Transform Cardiorespiratory Coherence

Introduction

Presence of an anaesthesiologist or an anaesthesia assistant supervised by an anaesthesiologist is considered to be the sole essential monitor for any general or major regional anaesthesia [1]. However, for most anaesthesia performed today, pulse oximeter, apparatus to measure blood pressure, electrocardiography, capnography, agent-specific anaesthetic gas monitor and peripheral nerve stimulator are considered standard of care. Traditionally, intraoperative drug administration has been guided by measurement of heart rate, arterial blood pressure, diaphoresis, lacrimation and movement. Depth of anaesthesia monitoring has not been adopted as required. It's ability to decrease the risk of awareness is still controversial [2]. Due to the low incidence of the event, relying on a minimal alveolar concentration of inhaled anaesthetic agents to prevent intraoperative awareness is considered by many as almost as effective in the everyday clinical practice. Fine adjustment in depth of anaesthesia may however seem desirable. Indeed, an excessive depth of anaesthesia may be associated with a poorer prognosis. When performing a propensity score analysis on data of a large randomized controlled trial (RCT), Leslie K., *et al*. found that the hazard ratio for death in patients who recorded bispectral (BIS) index values < 40 for > 5 minutes could be higher (1.41; 95% confidence interval [CI] 1.02 to 1.95) than the one of patients who did not experienced those low intraoperative BIS values [3].

More recently, a new class of monitor has emerged: the pain monitors. As opposed to monitors of depth of anaesthesia who aim to avoid intraoperative awareness, these new monitors measure the "nociceptive stimulus suppression level". In other words, their goal is to ensure appropriate blockage of the body reaction to a nociceptive stimulus. Insufficient intraoperative analgesia has been associated with higher intraoperative release of stress markers, postoperative inflammatory markers, postoperative pain scores, opioids requirements, coagulopathy and blood losses [4,5]. The role of pain monitors is to help titrate just the right dose of opioids (or any other analgesic drug) administered intraoperatively.

At a time when constraints on health care system's budgets are high, clear benefits of new monitoring devices must be demonstrated before considering their implementation in the everyday clinical practice. Recommendations to adopt a new device should be based on quality of evidence, balance between desirable and undesirable effects, values and preferences but also on whether or not the new device represents a wise use of resources [6,7]. Therefore, this review was undertaken to look for evidence of benefits that can be added by introducing pain monitors in the clinical practice.

Materials and Methods

For the purpose of the review, a pain monitor was defined as any device or method applied to identify a nociceptive stimulus. A search for clinical trials evaluating a pain monitor in humans was conducted in PubMed, CENTRAL and Scopus in December 2017 with the following key words: pain monitor (Figure 1). References lists of related reviews were checked. There was no language or publication status restriction applied. Trials evaluating these devices for other purposes (such as depth of anaesthesia), searching for possible confounding factors on the efficacy of those devices or aiming at physiologic explanations were not retained. Case reports were also rejected.

Results and Discussion

One thousand and seventeen abstracts were screened (Figure 1). One hundred and thirty-eight trials were selected for further examination. Nineteen were excluded for the following reasons: two case reports, ten because evaluating a pain monitor was not the goal of the trial, two references could not be located, three trials examined possible effects of confounding factors on accuracy of the monitor and two articles were explaining the development of the technology (Figure 1). The one hundred and nineteen trials retained are summarized in table 1 and table 2.

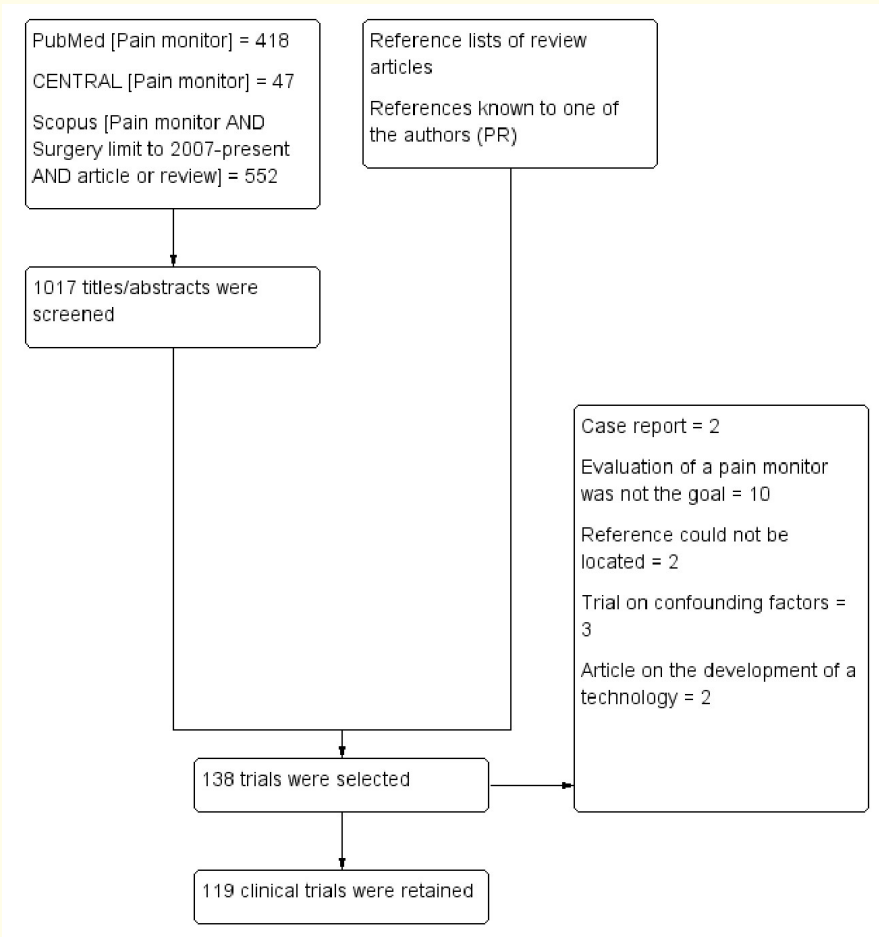

Figure 1: *Selection of trials.*

Study	Monitor/comparison	Study design	Population	Findings (author's conclusions)
Bispectral index (BIS)				
Arbour 2015 [7]	BIS	Prospective	25 critically ill adults with traumatic brain injury Turning	Findings support the potential use of the bilateral BIS for pain detection in nonverbal patients with traumatic brain injury
Bonhomme 2006 [8]	BIS and AAI	RCT Randomized to the analgesic regimen	23 adults undergoing lumbar arthrodesis under sevoflurane GA adjusted for BIS 40 to 60 Epidural analgesia with ropivacaine and clonidine or saline	AAI response to the onset of surgical stimulation significantly differs according to the analgesic regimen
Gelinas 2011 [9]	BIS and CPOT	Prospective	9 mechanically ventilated patients	Both the BIS index and the CPOT score were found to increase when patients were exposed to procedures compared with rest, and were found to be more sensitive to procedures compared with vital signs
Guignard 2000 [10]	BIS	RCT Randomized to remifentanil concentrations	50 adults Propofol and remifentanil GA Laryngoscopy	BIS is as sensitive as hemodynamic responses after a painful stimulus for detecting deficits in the analgesic component of anaesthesia
Hans 1999 [11]	BIS	RCT Randomized to sufentanil blood concentrations	20 adults undergoing neurosurgery Propofol and sufentanil GA Mayfield pin insertions	BIS response to noxious stimulation is modulated by the analgesic regimen
Kearse 1994 [12]	BIS and EEG	Prospective	44 adults (21 to 67 years) scheduled for non cranial surgery Propofol and nitrous oxide GA	BIS was more accurate than standard power spectrum parameters in predicting movement in response to skin incision
Li 2009 [13]	BIS	Prospective	48 sedated, ventilated cardiac surgery patients	Significant changes in heart rate, pupil size, and BIS occurred with the noxious procedure but not with the non-noxious procedure
Sebel 1995 [14]	BIS	Prospective/Retrospective	42 adults Isoflurane GA	BIS may be a useful predictor of whether patients will move in response to skin incision during anaesthesia with isoflurane/oxygen
Vernon 1995 [15]	BIS and EEG	RCT Randomized to the anaesthetic regimen	50 adults Isoflurane alfentanil GA or Propofol alfentanil GA	BIS was a better predictor of patient response than haemodynamic status
CARDEAN				
Cividjian 2007 [17]	CARDEAN and BIS	Retrospective	40 adults undergoing knee surgery Propofol for BIS < 60 and remifentanil GA	Retrospectively, a cardiovascular index predicted unexpected intraoperative movements
Martinez 2010 [18]	CARDEAN and BIS	RCT Randomized to access to CARDEAN values or not	159 adults (20 to 75 years) scheduled for colonoscopy Propofol GA adjusted for BIS values between 40 and 60 Alfentanil according to haemodynamic variables	With BIS <60, CARDEAN-guided opioid administration is associated with a reduction of 51% of clinically unpredictable movements in unparalyzed patients undergoing colonoscopy
Rossi 2012 [19]	CARDEAN	RCT Randomized to the remifentanil blood concentrations	18 adults undergoing spinal disc repair Propofol for BIS between 40 and 60 and remifentanil	Changes in CARDEAN appeared linked to adequacy of antinociception
Composite variability index (CVI)				
Ellerkmann 2013 [20]	CVI BIS and FEMG	Prospective	24 patients Propofol and remifentanil Tetanic stimulation	Changes in CVI and EMG might help identify inadequately low levels of analgesia
Mathews 2012 [21]	CVI	Prospective	120 adults undergoing elective non cardiac surgery Propofol/sevoflurane for BIS between 45 and 60 GA	CVI increases before somatic events began earlier than heart rate changes and may provide caregivers with an early warning of potentially inadequate antinociception
Sahinovic 2014 [22]	CVI	RCT Randomized to the anaesthetic regimen	120 adults undergoing surgery Propofol for BIS 30, 50 or 70 and various remifentanil concentrations GA	CVI appears to correlate with somatic responses to noxious stimuli However, unstimulated CVI depends more on hypnotic drug effect than on opioid concentration
Shoushtarian 2016 [23]	CVI	RCT Randomized to the anaesthetic regimen	80 patients GA including remifentanil	Combining electroencephalographically derived hypnotic and analgesic quantifiers may enable better prediction of patients who are likely to respond to tetanic stimulation
Von Dincklage 2012 [24]	CVI, NFRT, NSRI and BIS	Prospective	50 women Propofol and remifentanil GA	We conclude that the NFRT best predicts movement and heart rate responses to noxious stimuli
Electrocardiogram				
Rantanen 2007 [25]	Electrocardiogram	Prospective	Adults undergoing open abdominal surgery Propofol and remifentanil GA Tetanic stimulation	RR interval responses to painful stimuli were prominent and decrease at high remifentanil concentrations

Singham 2003 [26]	Electrocardiogram	Prospective	31 women undergoing gynaecologic surgery GA	Variations in pulse transit time reflects autonomic response to nociceptive stimulation and fluctuations in anaesthetic depth independently of heart rate
Electroencephalogram (EEG)				
Bolanos 2016 [27]	EEG Poincaré plot	Prospective	Patients undergoing minimally invasive medical procedures	Models including parameters from Poincaré plot emerge as a good estimator of sedation-analgesia levels
Jensen 2014 [28]	EEG (qCON and qNOX) and BIS	Prospective	60 ambulatory surgery patients Propofol and remifentanil GA	The qNOX showed significant overlap between movers and non-movers, but it was able to predict whether or not the patient would move as a response to noxious stimulation, although the anaesthetic concentrations were similar
Melia 2015 [29]	EEG and BIS	Retrospective	Database study 378 adults who had ulrasonographic endoscopy Propofol and remifentanil sedation	The proposed measures exhibit better performances than BIS
Melia 2017 [30]	EEG (qCON and qNOX)	Prospective	140 patients Propofol and remifentanil GA	qNOX has a better predictive value for response to noxious stimulation
Seitsonen 2005 [31]	EEG	Prospective	31 women undergoing abdominal hysterectomy Sevoflurane and fentanyl GA	Combination of information from different sources may be required for monitoring the adequacy of analgesia during anaesthesia
Zhang 2012 [32]	EEG	Prospective	7 volunteers Noxious radiant-heat stimuli	Gamma band oscillations recorded over primary somatosensory cortex predict the subjective pain intensity, even when saliency is reduced by repetition
Evoked potentials (EP)				
Schmidt 2007 [33]	EP	Cross-over design	10 healthy men Propofol, remifentanil or placebo	Long latency components of the somatosensory EPs are differently affected by remifentanil and propofol administration
Fascial electromyography (FEMG)				
Edmonds 1988 [34]	FEMG	Prospective /Retrospective	7 volunteers and adults (18 to 69 years) undergoing elective arthroscopic surgery Isoflurane and fentanyl GA	During periods of elevated facial muscle activity, fentanyl or butorphanol decreased FEMG amplitude

Mathews 2007 [35]	Entropy	Prospective	60 patients (40 for development set and 20 for validation) Anterior cruciate ligament repair Propofol and remifentanil GA	This feasibility study supports the concept that remifentanil may be delivered using an algorithm that maintains the difference between state entropy and response entropy between the upper and lower boundary condition
Takamatsu 2006 [36]	Entropy	Prospective	40 women Sevoflurane GA Electrical stimulation Propofol and fentanyl	Noxious stimulation increased the difference between response entropy and state entropy However, an increase in the difference does not always indicate inadequate analgesia and should be interpreted carefully during anaesthesia
Tewari 2016 [37]	Entropy	RCT Randomized to drugs titrated as per entropy values or standard care	120 women coming for transvaginal oocyte retrieval	Intraoperative entropy-guided drug administration decreased analgesia requirement in the postoperative care unit
Valjus 2006 [38]	Entropy	RCT Randomized to esmolol or remifentanil	51 women undergoing gynaecological laparoscopic surgery	In patients undergoing gynaecological laparoscopic day-case surgery, activation of response entropy seems not to be more sensitive than state entropy in guiding the use of opioids during general anaesthesia
Wheeler 2005 [39]	Entropy	Prospective	20 adults undergoing spinal surgery Isoflurane GA	We conclude that increased response entropy during painful stimulation was not dependent on recovery from paralysis but was seen more often in patients anaesthetized with 0.8% compared with 1.4% isoflurane This suggests that response entropy reflects FEMG and may be useful to identify inadequate anaesthesia and patient arousal during painful stimuli
Yli-Hankala 1994 [40]	FEMG, EP, EEG and heart rate	Prospective	12 patients Isoflurane GA	Both the auditory steady state evoked potential and FEMG showed significant increases in amplitude during the last 5-min period before movement Heart rate did not change before movement
H-Reflex				

Rehberg 2004 [62]	H-Reflex and BIS	Prospective	12 women Sevoflurane GA Tetanic stimulation	Suppression of movement to noxious stimulation and suppression of H-reflex amplitude by sevoflurane follow similar concentration–response functions Although this does not imply a causal relation, it explains the high predictive value of H-reflex amplitude for motor responses to noxious stimuli, even in a narrow concentration range around the $MAC_{tetanus}$
Heart rate variability (HRV)				
Boselli 2013 [47] NCT01633320	ANI	Prospective	200 adults (18 to 75 years) Surgery or endoscopy Propofol, remifentanil and ketamine GA	A negative linear relationship was observed between ANI immediately after arousal and VAS scores on arrival in PACU
Boselli 2014 [48] NCT01796249	ANI	Prospective	200 adults (18 to 75 years) ENT and orthopaedic lower limb surgery Halogenated-based and remifentanil GA	A negative linear relationship was observed between ANI immediately before extubation and VAS scores on arrival in PACU
Boselli 2015 [49] NCT01796210	ANI versus BIS	Prospective	50 adults (18 to 75 years) undergoing suspension laryngoscopy Propofol and remifentanil GA	ANI predicted haemodynamic reactivity during laryngoscopy better than BIS
Boselli 2016 [50]	ANI	Prospective	120 patients undergoing ENT and orthopaedic lower limb surgery Desflurane and remifentanil GA	Dynamic variations of ANI provide better performance than static values to predict haemodynamic reactivity during desflurane/ remifentanil GA
Gruenewald 2013 [51] NCT01522508	ANI and SSI	Prospective	25 adults (18 to 65 years) undergoing elective surgery Propofol and remifentanil GA Tetanic stimulation	ANI and SSI consistently reflected nociceptive stimulation but did not predict movement to stimulation
Gruenewald 2015 NCT01522508 [52]	ANI and SSI	Prospective	25 adults undergoing surgery Sevoflurane and remifentanil GA	ANI and SSI reflected nociceptive stimulation
Janda 2013 [41]	HRV	Prospective	10 adult patients scheduled for trauma surgery	The control system, reflecting the level of analgesia during general anaesthesia designed and evaluated in this study, allows for a clinically practical, nearly fully automated infusion of an opioid during medium-length surgical procedures with acceptable technical requirements and an adequate precision
Jeanne 2009 [42]	HRV	Prospective	49 adults Propofol and sufentanil, alfentanil or remifentanil GA	The nociception–analgesia balance is a direct determinant of HRV during surgical anaesthesia

Jeanne 2012 [53]	ANI versus heart rate and arterial blood pressure	Prospective	15 adults undergoing laparoscopic appendectomy or cholecystectomy Propofol for BIS 40 to 60 and remifentanil on haemodynamic parameters Tetanic and surgical stimulations	ANI seems more sensitive than heart and systolic blood pressure to moderate nociceptive stimuli in propofol anaesthetized patients
Jeanne 2014 [54]	ANI versus heart rate and arterial blood pressure	Prospective	27 adults undergoing total knee replacement Propofol and sufentanil	ANI measures during propofol anaesthesia are coherent with the evolution of the analgesia/nociception balance, although its performance decreases in awake patients
Latson 1993 [43]	HRV	RCT Randomized according to the anaesthetic regimen	26 women undergoing laparoscopic tubal ligation Isoflurane or propofol GA	Surgical stimulation may have significant effects on the autonomic reflexes mediating HRV, and such effects vary with anaesthetic technique
Ledowski 2013 [55] ACTRN12612001193864	ANI versus VAS scores	Prospective	120 postoperative patients	ANI did not reflect different states of acute postoperative pain measured on a VAS scale after adult sevoflurane-based general anaesthesia
Ledowski 2014 [56] ACTRN12613000212752	ANI	Prospective	30 adults undergoing surgery Sevoflurane GA	ANI appears to reflect different levels of stimulation during sevoflurane-based general anaesthesia However, it was of little predictive value to preempt significant haemodynamic changes
Le Guen 2012 [57]	ANI versus VAS	Prospective	45 parturients who requested epidural analgesia	ANI has an inverse linear relationship with VAS pain scores
Logier 2006 [44]	HRV	Retrospective	39 patients under GA	Our parameters at different levels of analgesia during surgical stimulation were related to pain/analgesia and relatively independent from other anaesthesia related events like hypnosis and haemodynamic conditions
Rantanen 2006 [45]	HRV, entropy and photoplethysmography	Prospective	55 women operated under Propofol and remifentanil GA	HRV, difference entropy and photoplethysmography were among the predictor of the nociceptive–anti-nociceptive balance at skin incision
Sesay 2015 [46]	HRV and VAS scores	Prospective	120 adults having undergone minor spinal surgery Postoperative pain	HRV parameters are significantly correlated with VAS scores
Upton 2017 [58]	ANI	RCT Randomized to Intraoperative ANI-guided opioid or standard care	50 adults undergoing lumbar discectomy (18 to 75 years Sevoflurane GA)	ANI-guided fentanyl administration during sevoflurane anaesthesia for lumbar discectomy and laminectomy demonstrated decreased pain in the recovery room
Nociceptive flexion reflex threshold (NFRT)				

Von Dincklage 2009 [67]	NFRT (RIII) and BIS	Prospective	15 male volunteers Propofol GA Tetanic stimulation	Movement responses to noxious stimuli under propofol can be predicted by NFRT with a comparable accuracy as the BIS NFRT seems to be influenced by hypnotic effects
Von Dincklage 2010 [68]	NFRT (RIII) and BIS	Prospective	20 male volunteers Propofol and remifentanil Tetanic stimulation	NFRT and BIS are both influenced dose-dependently by remifentanil at those concentrations that suppress reactions to noxious stimuli The susceptibility of the parameters to remifentanil concentration seems to be of a similar quality Under different ratios of propofol and remifentanil concentrations, the NFRT threshold correlates with non-responsiveness better than the BIS
Nociception Level (NOL)				
Ben-Israel 2013 [64]	NOL	Prospective	25 adults scheduled for surgery	These results demonstrate the superiority of multi-parametric approach over any individual parameter in the evaluation of nociceptive response In addition, advanced non-linear technique may have an advantage over ordinary linear regression for computing NOL index Further research will define the usability of the NOL index as a clinical tool to assess the level of nociception during general anaesthesia
Edry 2016 [65]	NOL	Prospective	58 patients undergoing surgery	The NOL index changes proportionately with patients' response to various clinical and experimental noxious stimuli and discriminates noxious from nonnoxious stimuli with high sensitivity and specificity The NOL index also responds progressively to increasing stimuli intensity and is appropriately blunted by analgesic administration The NOL index was superior to other compared measures and appears to accurately characterize nociception during general anaesthesia

Martini 2015 [66]	NOL	Prospective	72 adults Propofol for BIS 45 and various remifentanil blood concentrations GA	NOL is a reliable measure of moderate and intense noxious stimulation and outperforms heart rate and mean arterial blood pressure in differentiating noxious from nonnoxious stimuli NOL was not affected by hemodynamic effects of remifentanil
Noxious stimulation response index (NSRI)				
Luginbühl 2010 [63]	NSRI, BIS and EP	Retrospective	44 women Propofol and remifentanil GA Tetanic stimulation	NSRI conveys information that better predicts the analgesic component of anaesthesia than EP, BIS, or predicted propofol or remifentanil blood concentrations
Pupillary reflex dilatation (PRD)				
Abad 2016 [69]	PRD	RCT Randomized to intraoperative analgesia guided by PDR or standard care	59 adults undergoing abdominal hysterectomy Intravenous GA	Monitoring of the intraoperative analgesia by pupillometry was able to reduce the intensity of the acute postoperative pain and analgesic consumption in the first 12 hours in the hospital room after major gynaecological surgery
Aissou 2012 [70]	PRD and PLRA	Prospective	100 adults Cholecystectomy, colonic surgery, abdominal wall surgery, upper abdominal surgery, and thyroidectomy Desflurane sufentanil and atracurium GA	In the immediate postoperative period, the PDR is significantly correlated with the VAS scores
Barvais 2003 [71]	PRD and BIS	Prospective	12 adults Propofol and remifentanil GA Tetanic stimulation	The decrease in pupil response to a painful stimulus is a better measurement of the progressive increase of remifentanil concentrations than haemodynamic or BIS measurements
Chapman 1999 [72]	PRD and EP		20 volunteers Noxious electrical stimulation	PRD increased significantly in peak amplitude as stimulus intensity increased
Guglielminotti 2013 [73]	PRD	Prospective	26 labouring women Epidural analgesia Uterine contractions	Changes in PRD and PLRA brought about by a uterine contraction may be used as a tool to assess analgesia in non-communicating patients
Guglielminotti 2015 [74]	PRD	RCT Randomized by remifentanil blood concentration	80 women undergoing vacuum aspiration Propofol and remifentanil GA Tetanic stimulation	PRD predicted movement
Huybrechts 2006 [75]	PRD	Prospective	13 patients undergoing thoracotomy Propofol and remifentanil GA Epidural analgesia	PRD-guided continuous thoracic epidural analgesia under low-dose remifentanil/propofol anaesthesia is feasible and ensures good postoperative analgesia

Isnardon 2013 [76]	PRD	Prospective	24 adults undergoing foot and ankle surgery Propofol and remifentanil GA Sciatic nerve block	The effects of peripheral nerve block can be detected via the measurement of PRD to noxious stimulation of the skin in patients receiving remifentanil
Kantor 2014 [77]	PLRA versus VAS scores	Prospective	145 adults Pain in PACU	Acute postoperative pain is not associated with pupillary diameter or PLRA
Larson 1993 [78]	PRD	RCT Randomized to the anaesthetic regimen	13 volunteers anaesthetized with either isoflurane or propofol Noxious electrical stimulation	The pupil is a more sensitive measure of noxious stimulation than the commonly used variables of arterial blood pressure
Larson 1993a [79]	PRD	Prospective	8 volunteers and 10 patients Combined isoflurane GA/ epidural analgesia	PRD was an accurate test of the sensory block level
Larson 1997 [80]	PRD	Prospective	6 volunteers submitted to the intervention on 4 consecutive days Isoflurane and alfentanil at four different target concentrations Noxious electrical stimulation	PRD in response to noxious stimulus is a measure of opioid effect in isoflurane anesthetized subjects PLRA is unaffected by alfentanil administration during isoflurane anaesthesia
Leslie 1996 [81]	PLRA, EEG and systolic arterial blood pressure	Prospective	10 healthy volunteers Propofol GA Tetanic electrical stimulation	EEG, PLRA and systolic arterial blood pressure predict movement
Oka 2007 [82]	PRD	Prospective	15 volunteers Various nitrous oxide concentrations Painful electrical stimulation	PRD may provide a useful indicator for studying the central processing of noxious stimuli and the effects of analgesic interventions
Sabourdin 2017a [83]	PRD	RCT Randomized to PRD- guided opioid administration or standard care	55 women undergoing gynaecologic surgery Propofol and remifentanil GA	The use of pupillometry to guide intraoperative analgesia reduced intraoperative remifentanil consumption and postoperative morphine requirements
Pulse wave reflex (PWR)				
Luginbiihl 2002 [88]	PWR	Prospective	Adults Sevoflurane GA Tetanic stimulation	An absent laser-Doppler skin vasomotor reflex does not predict a blunted arterial pressure or heart rate response to tracheal intubation The PWR may be a better predictor
Skin conductance				
Czaplik 2012 [89] DRKS00000755	NFSC versus standard monitors	RCT Randomized to epidural analgesia or saline	44 postoperative adults (> 18 years) GA lasting ≥ 90 minutes	The tested device failed to distinguish pain from other stressors in postoperative adult patients
Gjerstad 2007 [90]	NFSC and entropy	Prospective	20 women undergoing gynaecologic laparotomy Tetanic stimulation	NSCF was sensitive to tetanic stimuli at different opioid analgesic levels, by contrast with entropy

Gungor 2017 [91]	Skin conductance	Prospective	13 patients undergoing 25 lumbar sympathetic blocks	This preliminary study suggests that skin conductance is a more reliable and rapid response indicator of a successful sympathetic blockade when compared with traditional monitors
Ledowski 2006 [92]	NFSC versus VAS scores	Prospective	25 adult postoperative patients (18 to 85 years)	NFSC showed a significant correlation with the VAS scores whereas heart rate and blood pressure showed no or very weak correlation
Ledowski 2007 [93]	NFSC and VAS scores	Prospective	75 postoperative patients	May be a useful means of assessing postoperative pain
Ledowski 2009 [94]	NFSC and SSI versus VAS score	Prospective	100 adult postoperative patients	Both NFSC and SSI identified time points with moderate to severe pain with only moderate sensitivity and specificity
Ledowski 2010 [95]	NFSC, SSI, heart rate, blood pressure and hormone plasma levels	Prospective	20 adults scheduled for surgery Sevoflurane and fentanyl GA	Changes in SSI and NFSC only partially reflected changes in plasma noradrenaline levels SSI, heart rate and blood pressure, but not NFSC changed in response to changes in depth of analgesia by showing significant differences between before and after a bolus of fentanyl Predictive ability of both methods (NFSC and SSI) was poor
Loggia 2011 [96]	Skin conductance versus heart rate	Prospective	39 heathy male subjects Heat stimuli	At least for male subjects, heart rate provides a better predictor of pain perception than skin conductance
Naifeh 1983 [97]	Electrodermal responsivity	Prospective	Postoperative adults	The electrodermal response elicited by autonomic manoeuvres was significantly attenuated in postoperative patients but not in preoperative patients or in normal control subjects
Storm 2002 [98]	Skin conductance, BIS and catecholamine blood concentrations	Prospective	11 patients undergoing laparoscopic cholecystectomy Propofol and remifentanil GA	Skin conductance may be a useful method for monitoring the perioperative stress BIS did not show any stress response during tracheal intubation
Storm 2005 [99]	NFSC and BIS	Prospective	14 patients undergoing surgery	NFSC is sensitive to clinical stress during surgical stimulation
Surgical stress index (SSI)				
Ahonen 2007 [110]	SSI	RCT Randomized to esmolol or remifentanil adjusted to maintain systolic blood pressure within -20 to +10% of preoperative value	30 women undergoing gynaecologic laparoscopic surgery under desflurane GA	SSI was higher in patients receiving esmolol The index seems to reflect the level of surgical stress and may help guide the use of opioids during general anaesthesia

Bergman 2013 [111]	SSI	RCT Randomized to intraoperative opioids administered on SSI guidance or standard care	170 adults Propofol and remifentanil GA	Adjusting the remifentanil dosage according to the SSI in outpatient anaesthesia reduced the consumption of both remifentanil and propofol and resulted in faster recovery
Bonhomme 2011 [112]	SSI versus standard monitors	RCT Randomized according to the remifentanil target concentration (2, 4 and 6 ng/mL)	33 adults (18 to 80 years) undergoing neurosurgery Remifentanil analgesia for Mayfield pin insertions	SSI, heart rate and mean arterial blood pressure are of comparable value at gauging the balance between noxious stimulation and remifentanil blood concentration
Chen 2010 [113]	SSI versus standard monitors	RCT Randomized to SSI-guided analgesia versus standard practice	80 adults ENT surgery Propofol BIS adjusted GA Remifentanil adjusted on predicted blood levels versus SSI adjusted	SSI decrease remifentanil requirements and incidence of unwanted events defined as hypertension, tachycardia, somatic arousal (coughing, chewing, grimacing), somatic response (purposeful movement), hypotension or bradycardia
Gruenewald 2009 NCT00791791 [114]	SSI and BIS	Prospective	24 women undergoing elective gynaecological laparoscopy Sevoflurane and remifentanil GA	The SSI response to tetanic stimulation was dependent on the remifentanil concentration In 10 out of 63 cases, SSI detected response to stimulation, not detected by another variable SSI was unable to predict movement after stimulation
Heyse 2014 [115] NCT00522587	SSI and entropy	Secondary analysis from a RCT	40 adult patients (18 to 60 years) undergoing surgery Sevoflurane and remifentanil GA	SSI did not result in plausible parameter estimates, neither before nor after stimulation Significant population variability exists for CVI and SSI
Huiku 2007 [116]	SSI	Prospective	72 women undergoing gynaecologic or breast surgery Propofol and remifentanil GA	SSI reacts to surgical nociceptive stimuli and analgesic drug concentration changes during propofol–remifentanil anaesthesia
Ilies 2010 [117]	SSI	Prospective	71 patients undergoing surgery under GA, RA with or without sedation	In fully awake patients under spinal anaesthesia, the SSI does not reflect the nociception–antinociception balance This may be due to the influence of mental stress on the sympathetic nervous system Even light sedation attenuates these influences
Ledowski 2016 ACTRN12615000804583 [118]	SSI	Prospective	70 adults Postoperative pain	SSI values are predictive of postoperative pain only if obtained before patient arousal

Struys 2007 [119]	SSI	RCT Randomized to anaesthetic regimen	40 women Propofol and remifentanil GA	SSI appeared to be a better measure of nociception–anti-nociception balance than heart rate, entropy or pulse wave amplitude
Thee 2015 [120]	SSI and VAS scores	Prospective	100 adults scheduled for surgery	Sensitivity and specificity of SSI to discriminate between low, moderate and severe pain levels was moderate Both VAS scores and SSI correlated significantly with total opioid consumption
Wennervirta 2008 [121]	SSI and entropy	RCT Randomized to RA and GA or GA alone	26 adults undergoing shoulder surgery Desflurane GA	SSI values were lower in patients with plexus block covering the sites of nociceptive stimuli In detecting nociceptive stimuli, SSI had better performance than heart rate, blood pressure, or entropy
Yli-Hankalal 2006 [122]	SSI	RCT Randomized to ropivacaine or saline epidural	30 patients undergoing abdominal surgery Sevoflurane GA	SSI is sensitive to ropivacaine mediated epidural antinociception after skin incision, but this sensitivity disappears within 20 minutes
Skin vasomotor reflex (SVmR)				
Shimoda 1998 [109]	SVmR	RCT Randomized to SVmR or standard care	44 adults Sevoflurane 1.0 or 1.3 MAC GA Electrical stimulation	SVmR provides useful information for determining optimal anaesthetic depth for laryngoscopy and intubation

Table 1: *Adult trials.*

AAI: a-Line Autoregressive Index; ANI: Analgesia/Nociceptive Index (an index derived from an HRV analysis according to a specific algorithm); BIS: Bispectral Index; CARDEAN: Beat-by-beat arterial blood pressure changes combined with an algorithm that detects hypertension followed by tachycardia and produces an index scaled 0 to 100; CPOT: Critical-Care Pain Observation Tool; CVI: Composite Variability Index; EEG: Electroencephalogram; EMG: Electromyography; ENT: Ear, Nose and Throat; EP: Evoked Potentials; FEMG: Facial Electromyography; GA: General Anaesthesia; HRV: Heart Rate Variability; MAC: Minimal Alveolar Concentration; NOL: Nociception Level; NSRI: Noxious Stimulation Response Index; NFRT: Nociceptive Flexion Reflex Threshold; NFSC: Number of Fluctuations in Skin Conductance; PACU: Postanaesthesia Care Unit; PLRA: Pupillary Light Reflex Amplitude; PRD: Pupillary Reflex Dilatation; PWR: Pulse Wave Reflex; RA: Regional Anaesthesia; RCT: Randomized Controlled Trial; SVmR: Skin Vasomotor Reflex; SSI: Surgical Stress Index; VAS: Visual Verbal Analogical Pain Score

Study	Monitor/comparison	Study design	Population	Findings (author's conclusions)
Bispectral index (BIS)				
Lim 2017 [16] UMIN000010545	BIS	RCT Randomized to injection at loss of eye lash versus at BIS < 40	135 healthy children (3 to 12 years) scheduled for minor elective surgery Thiopental induction dose Pain to rocuronium injection	BIS values < 40 reduce the incidence of withdrawal movement at rocuronium injection
Heart rate variability (HRV)				
Avez-Couturier 2016 [60]	ANI, heart rate and FLACC scale	Prospective	26 children (6 months to 18 years) undergoing biopsy under analgesia and light sedation	ANI measurement seems relevant in paediatric procedural pain, across age
Migeon 2013 [61]	ANI and PDR	Prospective	58 children operated under sevoflurane GA/RA	Both PDR and ANI rapidly change after skin incision in case of RA failure
Sabourdin 2013 [62]	ANI and skin conductance	Prospective	12 children undergoing middle-ear surgery Desflurane for BIS 50 and remifentanil GA Tetanic stimulation	ANI might provide a more sensitive assessment of nociception in anaesthetized children than haemodynamic parameters or skin conductance
Pupillary reflex dilatation (PRD)				
Connelly 2014 [85]	PRD versus pain scales	Prospective	30 children (9 to 17 years) who had elective surgical correction of pectus excavatum	The association of both maximum pupillary constriction velocity and diameter with pain scores illustrates the potential for using pupillometry as a non-invasive method to objectively quantitate pain response/intensity in children
Constant 2006 [86]	PRD versus BIS	Prospective	24 children (2 to 15 years) Sevoflurane GA	PRD is a more sensitive measure of noxious stimulation than the commonly used variables of heart rate, arterial blood pressure and BIS in children anaesthetized with sevoflurane
Emery 2004 [87]	PRD versus skin temperature	Prospective	20 children (10 months to 5 years) Sevoflurane GA Caudal analgesia	Skin temperature cannot be used to estimate sensory level during combined GA/caudal anaesthesia PRD of 0.2 mm is sensitive to the loss of analgesia but is not clinically useful PRD may be useful above 2 years of age
Sabourdin 2017 [88] NCT 02648412	PRD	Prospective	24 children from a burn care unit	In children, pupillary reflex dilation to nociceptive stimuli persists under deep sedation obtained with 1 mg/k of intravenous ketamine combined with a 0.3 mg/kg oral morphine premedication, and its magnitude depends on the intensity of the stimulation

Skin conductance				
Choo 2010 [100]	NFSC	Prospective	100 school-aged children (7 to 17 years) Pre- and postoperative measurements	NFSC measurement is feasible in a perioperative setting but was not specific for postoperative pain intensity and was unable to identify analgesia requirements when compared with self-report measures
Eriksson 2008 [101]	Galvanic skin response and PIPP	RCT Randomised to tactile or painful stimulation	32 full-term newborn undergoing blood sample	NFSC can differentiate painful from tactile stimulation, but more research is needed to achieve a clinically useful application
Gjerstad 2008 [102]	Skin conductance and modified COMFORT scale		20 mechanically ventilated children (1 day to 11 years) Endotracheal suctioning	Skin conductance showed better correlation with the increase in the modified COMFORT sedation score than heart rate and arterial blood pressure
Harrison 2006 [103]	Skin conductance	Prospective	20 hospitalized infants Heel lancing for blood sampling	Due to large variability in skin conductance activity further studies are needed before this technology can be recommended as a clinically useful indicator of pain and stress in neonates
Hellerud 2002 [104]	Skin conductance	Prospective	71 infants (premature and neonates) Heel prick for blood samples, or immunization	Non-painful sensory stimulation of infants, especially the newborn and preterm ones, can produce equal or higher levels of physiological stress activation than painful stimulation
Hullet 2009 [105] ACTRN12607000474459	NFSC	Prospective	180 postoperative paediatric patients (aged 1 to 16 years)	NFSC accurately predicted the absence of moderate to severe pain in postoperative paediatric patients
Painter 1965 [106]	Galvanic skin response	Prospective	61 children (2.5 to 15 years) Organic pain (present/absent at the time of evaluation), non-organic pain and controls	Organic and non-organic pain in children are differentially diagnosed by interesting and objective findings utilizing the galvanic skin response Children with organic pain are found to adapt quickly to a shock to the calf, whereas normal children continue to respond to a series of ten such shocks Children with non-organic pain show galvanic skin response patterns typical of normal control patients

Solana 2015 [107]	Skin conductance and BIS	Prospective	61 critically ill children (1 month to 16 years) mainly post cardiac surgery Painful procedure	Skin conductance was not found to be more sensitive or faster than clinical scales for the assessment of pain or stress in critical children undergoing painful procedures Skin conductance was not useful in muscle relaxed children
Storm 2000 [108]	Skin conductance	Prospective	20 preterm infants (gestational age ≥ 29 weeks) Heel stick	Spontaneous skin conductance activity reflects the stress response to Heel stick in premature infants from at least 29 weeks of gestational age
Surgical stress index (SSI)				
Kallio 2008 [123]	SSI and entropy	RCT Randomized to Topical anaesthesia with lidocaine and levobupivacaine versus saline	22 children (4 to 7 years) undergoing strabismus surgery GA	SSI, entropy and response entropy, heart rate and non-invasive systolic blood pressure detect autonomic responses to nociceptive stimuli in anaesthetized children undergoing strabismus surgery
Wavelet transform cardiorespiratory coherence (WTCRC)				
Brouse 2011 [124]	WTCRC		39 paediatric patients receiving GA	The WTCRC algorithm shows promise for noninvasively monitoring nociception during general anaesthesia, using only heart rate and respiration
Brouse 2013 [125]	WTCRC		48 children receiving GA for dental surgery	A nociception index based on cardiorespiratory coherence is more sensitive to nociception and antinociception than are mean heart and mean noninvasive blood pressure

Table 2: *Paediatric trials.*

ANI: Analgesia/Nociceptive Index (an index derived from an HRV analysis according to a specific algorithm); BIS: Bispectral Index; FEMG: Facial Electromyography; FLACC: Face Legs Activity Cry Consolability Scale; GA: General Anaesthesia; HRV: Heart Rate Variability; NFSC: Number of Fluctuations in Skin Conductance; PIPP: Premature Infant Pain Profile: PRD: Pupillary Reflex Dilatation; RA: Regional Anaesthesia; SSI: Surgical Stress Index; WTCRC: Wavelet Transform Cardiorespiratory Coherence

Bispectral index (BIS)

Adult data on BIS as a pain monitor

Nine trials published between 1995 and 2015 evaluated the BIS monitor as a pain monitor [7-15]. The majority of trials included found some value to the BIS monitor as a method to identify painful stimuli.

Paediatric data on BIS

One randomized controlled trial (RCT) found that withdrawal reaction to rocuronium injection was decreased in children with a BIS < 40 [16].

CARDEAN

Three trials published between 2007 and 2012 evaluated CARDEAN in adults [17-19]. One RCT with 159 participants under general anaesthesia and BIS < 60 reported that intraoperative CARDEAN-guided opioid administration reduced by 51% the incidence of unpredictable movements in unparalysed patients.

Composite variability index (CVI)

Five trials published between 2012 and 2014 [20-24] evaluated the CVI in adults. CVI appears to correlate with somatic response to noxious stimuli. However, unstimulated CVI depends more on hypnotic drugs than on opioid concentration.

Electrocardiogram

Two trials evaluated electrocardiographic modifications in response to noxious stimuli [25,26]. Singham., *et al*. reported that "variations in pulse transit time reflects autonomic response to nociceptive stimulation and fluctuations in anaesthetic depth independently of heart rate" [26].

Electroencephalogram

Six trials published between 2005 and 2016 [27-32] evaluated electroencephalographic modifications to painful stimuli. The qNOX was able to predict whether or not the patient would move [28].

Evoked potentials (EP)

Schmidt., *et al*. [33] reported that long latency components of the EPs are differently affected by remifentanil and propofol administration.

Fascial electromyography (FEMG)

Seven trials published between 1994 and 2016 [34-40] evaluated the response of FEMG to painful stimuli in adults either directly [34] or as entropy [35-40]. In a RCT, Tewari., *et al*. reported that intraoperative entropy-guided drug administration decreased analgesia requirement in the postanaesthesia care unit [37].

Heart rate variability [HRV]

HRV

Six trials published between 1993 and 2015 [41-46] evaluated HRV as a monitor of noxious stimulation. HRV parameters were significantly correlated with visual/verbal analogical (VAS) pain scores [46].

Analgesia/nociceptive index (ANI)

ANI is an index derived from an HRV analysis according to a specific algorithm

Adult data on ANI

Twelve prospective trials published between 2012 and 2017 evaluated ANI in adult patients [47-58]. A negative linear relationship between VAS pain scores and ANI was found in three trials [47,48,57]. ANI consistently reflected nociceptive stimulation in patients under general anaesthesia but did not predict occurrence of unwanted movements [51]. Performance in awake patients was less consistent [54]. One RCT compared ANI-guided intraoperative opioid administration with standard care [58]. Study authors reported reduced postoperative pain scores and reduced postanaesthesia care unit analgesic requirements with ANI-guided intraoperative opioid administration.

Paediatric data on ANI

Three trials published between 2013 and 2016 evaluated ANI in the paediatric population [59-61]. All three trials confirmed the value of the monitor to reflect the nociception/analgesia balance. Sabourdin., *et al*. confirmed its ability to identified failed regional blocks in anaesthetized children [61].

H-Reflex

In a trial on 12 volunteers, Rehberg., *et al*. [62] reported that the H-Reflex was a good predictor of motor response to painful stimulation.

Noxious stimulation response index (NSRI)

One trial [63] found that NSRI was a better predictor of analgesic component of anaesthesia than EP, BIS or predicted blood concentrations of propofol or remifentanil.

Nociception level (NOL)

Three trials published between 2013 and 2016 evaluated NOL as a pain monitor [64-66]. NOL is a mutiparametric monitor. All three trials reported that NOL could differentiated between noxious and nonnoxious stimulation with different degree of success. The trial with the smallest financial conflict of interest ([66]; Medasense Biometrics Ltd. (Ramat Yishai, Israel) provided the hardware and software used in the study; one author received consultancy fee from Medasense Biometrics Ltd. (Ramat Yishai, Israel) and the other authors declare no competing interests) reported a receiver operating characteristic curve (ROC) at a specificity of 75% of 0.66 for heart rate, 0.73 for mean arterial blood pressure and 0.82 for NOL [66]. ROC curves at a specificity of 75% for changes in heart rate, mean arterial blood pressure and NOL were 0.84, 0.78 and 0.95, respectively.

Nociceptive flexion reflex (NFRT)

Two trials from the same group published in 2009 and 2010 reported on NFRT as a pain monitor in volunteers [67,68]. Advantages of NFRT over BIS were unclear.

Pupillary reflex dilatation (PRD)

Adults data on PRD

Fifteen trials published between 1993 and 2016 evaluated PRD as a pain monitor in adults [69-83]. Two of these trials were randomized to intraoperative PRD-guided opioid administration versus standard care [69,83]. Intraoperative PRD-guided opioid administration reduced acute postoperative pain and analgesic requirement during the first hours after surgery [69,83].

Paediatric data on PRD

Four trials evaluated PRD as a pain monitor in children [84-87]. PRD is a more sensitive measure of noxious stimulation than the commonly used variables of heart rate, arterial blood pressure and BIS in children anaesthetized with sevoflurane [85]. PRD remains useful in children sedated with ketamine 1 mg/kg [87].

Pulse wave reflex (PWR)

Luginbuhl., *et al*. [88] reported that PWR could be useful in predicting haemodynamic response to painful stimulation.

Skin conductance

Data on skin conductance in adults

Eleven trials published between 1983 and 2017 evaluated skin conductance as a pain monitor in adults [89-99]. Most authors found skin conductance as being of moderate interest.

Data on skin conductance in the paediatric population

Skin vasomotor reflex

Skin vasomotor reflex was evaluated by Shimoda., *et al*. in 1998 [109]. The authors concluded that skin vasomotor reflex helped them to determine the optimal anaesthetic depth required for laryngoscopy and intubation.

Surgical stress index (SSI)

Data on SSI in adults

Thirteen trials published between 2006 and 2014 [110-122] evaluated SSI as a pain monitor in adults. Two of these trials were randomized to intraoperative SSI-guided opioid administration versus standard care [111,113]. Study authors concluded that adjusting intraoperative opioid administration according to the SSI reduces intraoperative anaesthetic drug requirements and produces faster recovery.

Data on SSI in the paediatric population

Kallo., *et al*. published a small trial in children undergoing strabismus surgery [123]. Study authors concluded that SSI, FEMG, heart rate and non-invasive systolic blood pressure detect autonomic response to painful stimulation in this population.

Wavelet transform cardiorespiratory coherence (WTCR)

Two trials from the same group [124,125] reported on WTCR as a pain monitor in children. Study authors concluded that "A nociception index based on cardiorespiratory coherence is more sensitive to nociception and antinociception than are mean heart rate and mean non-invasive blood pressure".

Conclusion

This narrative review suggests that:

- The BIS monitor has some value to identify painful stimuli;
- In adults, CARDEAN-guided intraoperative opioid administration reduces the incidence of unpredictable movements in unparalysed patients;
- CVI appears to correlate with somatic response to noxious stimuli. However, unstimulated CVI depends more on hypnotic drugs than on opioid blood concentration;
- For EEG, the qNox can predict unwanted movements in unparalysed asleep adults;
- FEMG allows to distinguish between the analgesic and the hypnotic components of general anaesthesia in adults. Entropy-guided intraoperative drug administration decreases analgesia requirement in the postanaesthesia care unit;
- HRV correlates with pain scores in adults;
- In asleep adults, ANI (an index derived from HRV) reflects nociceptive stimulation but does not predict occurrence of unwanted movements;

- In awake adults, ANI is inversely correlated to pain scores but the performance of the monitor is less consistent than in asleep patients;
- ANI-guided intraoperative opioid administration reduces postanaesthesia care unit pain scores and analgesic requirements;
- In the paediatric population, ANI reflects the nociceptive/analgesia balance and can identify failed regional blocks in asleep children;
- NOL can differentiate noxious from nonoxious stimulation in adults;
- Intraoperative PRD-guided opioid administration reduces acute postoperative pain and early postoperative analgesic requirements in adults;
- In asleep children PRD is more sensitive to noxious stimulation than heart rate, blood pressure and BIS;
- Skin conductance has been reported as being of moderate interest in adults and in children;
- Intraoperative SSI-guided opioid administration reduces opioid consumption and produces faster recovery in adults undergoing ambulatory or ear, nose and throat surgery;
- In children, SSI is not superior to haemodynamic parameters to identify a painful stimulation.

In conclusion, it seems possible to identify a painful stimulation from a pain monitor. Various technologies have been studied. More RCTs comparing pain monitor-guided intraoperative drug administration with standard care are required before a cost/benefit ratio can be established.

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