A systematic review of methods to detect intra- and post-operative pain

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Background and Aims

Monitoring nociception-antinociception (NAN) balance during the surgery is essential for preventing unwanted intra-surgical events and decreasing post-surgical complications. However, the conventionally monitored signals (e.g., heart rate, blood pressure) showed lower than 80% accuracy to provide a reliable detection of nociception. This deficiency led to a requirement of exploring advanced methods for more objective monitoring. The aim of this project is to critically review the available methods designed for intraoperative nociception detection during the surgery. Moreover, a better intraoperative detection method may lead to more optimum analgesic dosage during the surgery. The effects of intraoperative analgesic dosage on intra- and post-operative pain conditions were also investigated, to testify the significance of detection methods of guided analgesic administration.

Methods

Two topics were discussed in this paper: 1) methods to detect intraoperative pain during the surgery; 2) effects of analgesic dosage administered during the surgery on intra- and post-operative pain. Two systematic review associated with these topics were performed in PubMed, Embase, Web of Science, and Cochrane Library. The search was limited to publication date in or after 2000. The reference lists of included studies were also screened. Titles and abstracts of retrieved articles were firstly filtered according to the inclusion and exclusion criteria. Full-text of eligible articles were downloaded and assessed for inclusion. To answer the first question (intraoperative pain detection methods), the type of the monitored signal, working principle, reliability, and limitations of the methods were collected. The second review included relevant randomized-controlled-trails (RCTs) on low-dose versus high-dose of remifentanil. The risk of bias of RCTs was checked through RoB2 tool, rejecting trials with high risk. A “vote counting” on trials’ favoured effect direction of dosage was conducted with summarizing key elements of extracted data in the form of tables.

Results

Based on 112 papers, 7 categories and a total of 19 nociception-monitoring methods were found. The categories are 1) Sympathetic tone-based: Surgical Stress Index (SSI), otherwise known as Surgical Pleth Index (SPI), Autonomic Nervous System Index (ANSSI), Pupillometry, Skin Conductance (SC), Cardiovascular depth of analgesia (CARDEAN) Index, Analgoscore, Nociceptive Response (NR) value, Arterial stiffness (K) index; 2) Parasympathetic tone-based: Analgesia Nociception Index (ANI); 3) Electroencephalography-based: Composite Variability Index (CVI), qNOX index, Response Entropy and State Entropy difference (RE-SE), A-Line Autoregressive Index (AAI), Somatosensory Evoked Potentials (SEP); 4) Combination indices: Nociception Level index (NoL), Response index of Nociception (RN), STeady-state index during general ANaesthesia (STAN); 5) Electromyogram–based: Nociceptive Flexion Reflex Threshold (NFRT); 6) Drug interaction models: Drug interaction parameter (U), Noxious Stimulus Response Index (NSRI); 7) Neuroimaging: functional near-infrared spectroscopy (fNIRS). The most commonly researched method is SPI, while the method with maximum accuracy was Pupillometry with 93.3% sensitivity and 100% specificity in detecting noxious stimuli. No methods was based on the human bio-fluids.

Twenty-two RCTs with 1412 patients were included for analysing the influence of intraoperative analgesic dosage on postoperative pain conditions. More than half of these trails (n=12) reported that a higher-dose results in either higher pain scores or higher cumulative postoperative analgesic consumption post the surgery.

Summary and Conclusions

This review showed that there is no method showing both 99% sensitivity and 99% specificity to detect intraoperative nociception during the surgery. Since high intraoperative analgesic dosage increased the probability of worse postoperative pain conditions, new methods are required to guide the analgesics dosage administration and improve pain outcomes.

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ABBREVIATIONS

AUC = area under the receiver operating characteristics curve

ECG = electrocardiography

EEG = electroencephalography

EMG = electromyogram

HRV = heart rate (HR) variability

IAD = intraoperative analgesics dosage

MAP = mean arterial pressure

NAN = nociception-antinociception

P(k) = prediction probability

PPGA = amplitude of photoplethysmograph (PPG) waveform

SBP = systolic blood pressure (BP)

INTRODUCTION

Background

The intraoperative balance of analgesia, otherwise known as nociception-antinociception (NAN) balance, is theoretically managed through monitoring nociception and administering of required analgesics. Maintaining balance during the surgery is important for surgical outcomes. Insufficient analgesia may lead to more intraoperative unwanted events (e.g., movement and increased hemodynamic instability). Excessive analgesia may cause opioid-induced complications such as postoperative vomiting and shivering (Figure.1) since the most commonly used analgesics used during the surgery are opioids (Lavand'homme and Steyaert, 2017). Acute-opioid-tolerance is a postoperative complication known as an adaptation to high-levels of opioid with a decreased sensitivity to the drug effects. Acute-opioid-tolerance increases the dosage required for early postoperative analgesia, which may result in opioid abuse and more induced side-effects secondarily (Colvin et al., 2019) (Figure.2). Therefore, the control of intraoperative dosage is the key to stop this vicious circle between opioid requirement and pain conditions. This control requires precise monitoring of NAN balance, which can be achieved by appropriate intraoperative nociception detecting methods.

Conventionally, anaesthetists monitor nociception during general anaesthesia through observing clinical responses (e.g., heart rate (HR), blood pressure (BP), movement) as signals. However, the conventional method highly relies on anaesthetists' experience, and the monitored clinical signs are inadequate to assess NAN balance due to great interference from other non-nociceptive confounders (e.g., consciousness, metabolism) (Lichtner et al., 2018). An overall less than 80% accuracy in detecting noxious conditions making conventional signals incompetent for intraoperative NAN monitoring (Funcke et al., 2017).

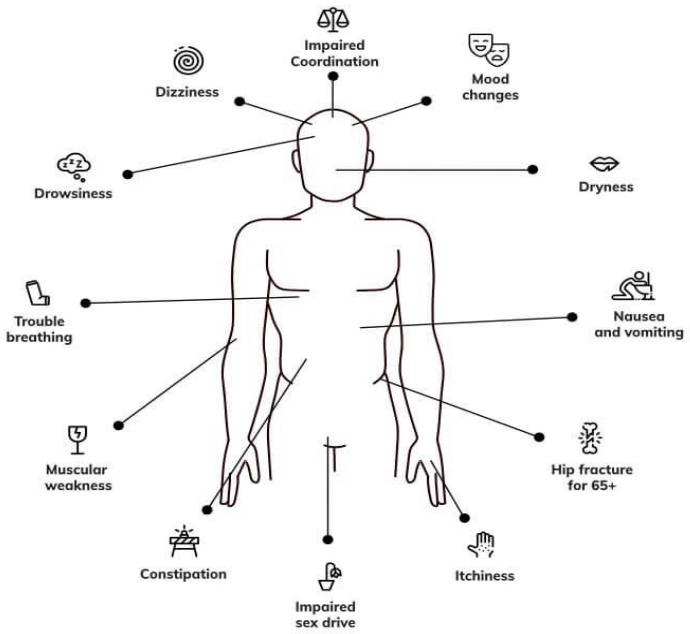


Fig. 1 Numerous complications of opioids. https://reachforthefacts.com.au/side-effects/

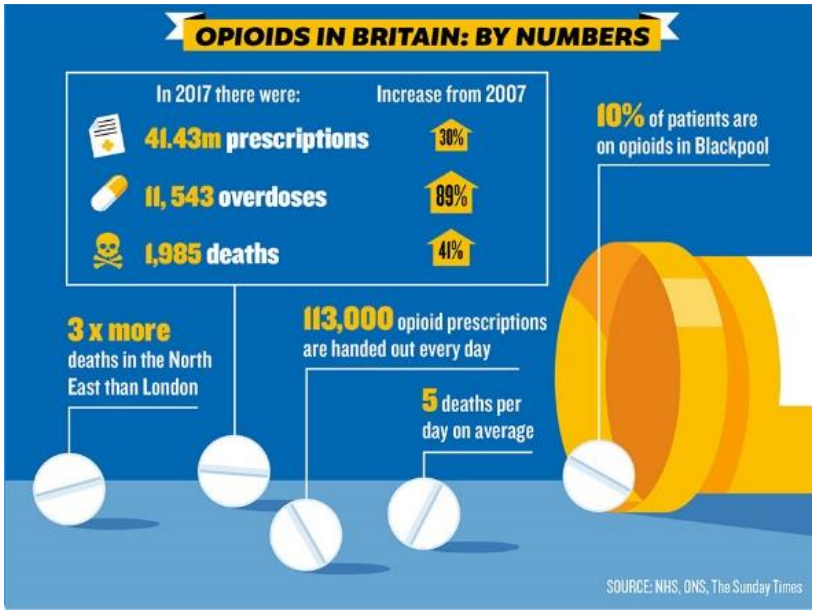


Fig.2 Opioids crisis, increased overdoses and abuse from 2017 in Britain. https://theday.co.uk/briefings/the-opioid-crisis

Evaluation and importance

The reliability of NAN monitoring was evaluated by the accuracy of detecting induced noxious stimuli, or responding to administered analgesics concentration (Martini et al., 2015). Two or more potential statistics, such as sensitivity, specificity, and prediction probability, are used to characterize accuracy (Leeflang et al., 2008). Sensitivity is defined as the induced noxious stimuli are correctly identified as nociception, while specificity is the non-noxious stimuli are correctly identified as non-nociception. High

sensitivity helps rule in all potential nociception, while high specificity reduces type I error of ruling in non-nociception (Altman and Bland, 1994). The receiver operating characteristics curve is used for detector performance. The area under curve (AUC) presents highlight the covariation between sensitivity and specificity. Prediction probability [P(k)] is analogous to AUC, presenting an overall characteristic of sensitivity and specificity. AUC and prediction probability ranges between 0.5 and 1, with a value of 0.5 means mere chance, and closer to 1 means better performance in predicting nociception-related response (Gatsonis and Paliwal, 2006). Correctly estimating NAN is key for guiding analgesics administration, thus, a 100% sensitivity and specificity is required to make sure fully discovering of insufficient antinociception, and no excessive analgesics administered when sufficient.

Objective

The objective of this project is to answer the following questions through systematic review of literature:

1. What are the the available methods to detect intraoperative nociception during the surgery and what are their limitations.
2. What is the influence of intraoperative analgesic dosages (IAD) on intra- and post-operative pain.

Hypotheses

In line with the above objectives, our hypotheses are:

1. There is no method detecting intraoperative pain during the operation with both 99% sensitivity and 99% specificity.
2. There is no method for detecting intraoperative pain during the operation that is based on the analysis of the human bio-fluids.
3. The higher dosage of remifentanil administered during the operation would lead to the worse postoperative pain conditions.

METHODS

The literature search was performed on online databases Web of Science, EMBASE (Ovid version), Cochrane Library, and PubMed for data extraction. The detailed

methods are demonstrated through the following two sections corresponding to the two systematic reviews.

Section 1. Methods to detect intraoperative nociception during the surgery.

To give a comprehensive demonstration of available methods, this section summarized the key elements of their design principle, reliability, and limitations.

Search strategy and article identification

The first computer literature search was performed on May 9th, 2020 on objective 1. The first search terms are: “intraoperative”, combines “detect” OR “monitor”, combines “nociception” OR “pain” with “AND”. The first search retrieved several relevant reviews to give clues of available detection methods.

Next, based on the retrieved information, I performed a more detailed second search on potential methods and nociception-related signals using the following keywords and MeSH terms:

“bispectral index” OR “spectral entropy” OR “state entropy” OR “response entropy” OR “qNOX index” OR “composite variability index” OR “nociceptive withdrawal reflex” OR “RIII-reflex” OR “nociceptive flexion reflex” OR “analgesia nociception index” OR “heart rate variability” OR “pupillometry” OR “pupillary pain index” OR “pupillary reflex dilatation” OR “plethysmographic index” OR “surgical pleth index” OR “surgical stress index” OR “CARDEAN” OR “skin conductance” OR “somatosensory evoked potentials” OR “noxious stimulation response” OR “parasympathetic tone activity” OR “sympathetic tone activity” OR “drug model” OR “Analgoscore” OR “nociception level index” OR “biomarker” OR “bio-fluid” OR “stress hormone” OR “neuroimaging” OR “near-infrared spectroscopy ”.

The first and second search results were combined with “AND”. The reference lists of included studies were also checked to avoid missing relevant articles.

Data extraction

The title and abstract was screened with the following inclusion and exclusion criteria.

Inclusion criteria

1. Describing methods designed for monitoring intraoperative nociception.

2. Describing methods able to assess nociception during surgery.
3. Reporting procedures under general anaesthesia.
4. Published in or after the year 2000

Exclusion criteria

1. I excluded studies performed on animals, patients with consciousness, pre- or post-operatively, or not peer-reviewed.
2. Additionally, since analgesia is one component of anaesthesia, some studies investigated the potential of anaesthesia-monitoring methods [e.g. bispectral index (BIS)] for analgesia monitoring. Relevant studies were included in this review.
3. There are also some studies using the detection-methods-guided intraoperative analgesics consumption as surrogate outcomes of monitoring accuracy, these studies were included.

No limitation were applied on language, article type, or study type.

Full text of papers eligible for selecting criteria were downloaded and assessed. Finally, 112 articles were included. The PRSIMA chart is shown in Figure. 3.

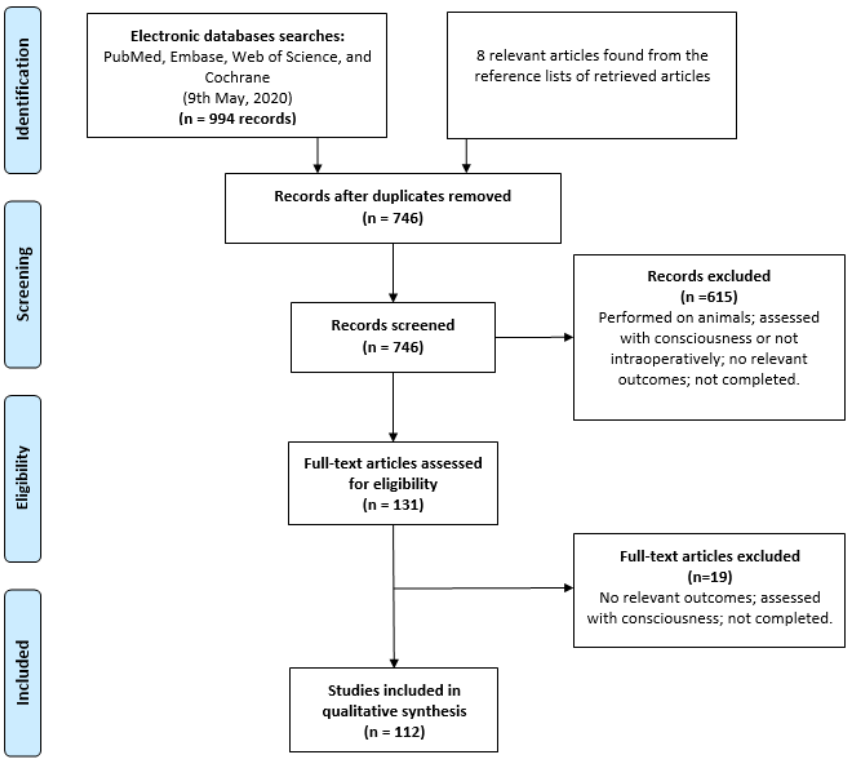


Fig. 3 The PRISMA flow of the article selecting process for the systematic review of methods to detect intraoperative nociception during the surgery.

Section 2. The influence of intraoperative analgesic dosages (IAD) on intra- and post-operative pain.

The effects of IAD on intraoperative pain was indicated by the extracted information from Section 1. In this section, a systematic review of the IAD influence on postoperative pain was carried out.

Measure of outcomes

The evaluation of influence was based on two aspects of pain outcomes:

1. Postoperative pain scores from patient-reported pain scales (higher score indicates worse pain condition)
2. Cumulative postoperative analgesics consumption (higher consumption indicates higher worse pain condition).

Search strategy and article identification

To minimize heterogeneity, I explored the influence of IAD by comparing two different intraoperative dosages of one specific analgesic. We only considered studies that use remifentanil, the most commonly used analgesics, for intraoperative analgesia maintenance. To improve the evidence level, I only extracted results from randomized controlled trials (RCTs).

A computer literature search was performed on June 30th, 2020. The search terms are: "surgery" OR "operation" OR "intra-operative" OR "post-operative", combine "pain" OR "nociception" OR "analgesia" OR "hyperalgesia" OR "drug adverse effects" OR “drug-related adverse reactions” OR “drug-related side effects” OR "patient-controlled analgesia", combine "dose" OR "dosage (administration)" OR "dose-response (relationship)" OR "drug dose sequence" OR “drug dose-response”, combine "remifentanil" with "AND". After removed duplicates, 911 records were identified.

Data extraction

Next, the title and abstract was screened with the following inclusion and exclusion criteria.

Inclusion criteria

1. RCTs, conducted under general anaesthesia.

2. Studied the relationship between intraoperative remifentanil dosage and postoperative pain.
3. Studied the remifentanil dose used for intraoperative anaesthesia maintenance.
4. Evaluated postoperative pain via scales and postoperative analgesics consumption.
5. Published in or after the year 2000.

Exclusion criteria

I excluded trials

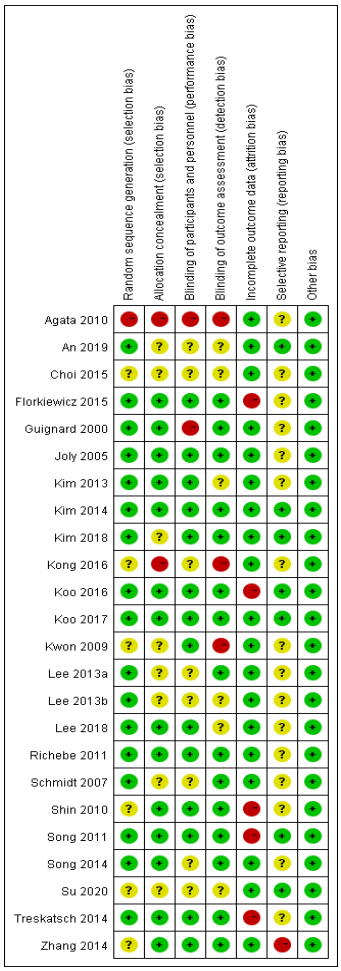
1. Performed on animals, or on patients with consciousness intraoperatively
2. Applied regional anaesthetic or local infiltration analgesia techniques
3. Not peer-reviewed

There was no limitation on surgery type and language.

Of these 911 records, 42 were included according to the selecting criteria and their full-text were downloaded and assessed. Finally, 23 trials were eligible.

Then an analysis of the risk of bias for RCTs was performed via Cochrane Risk of Bias Tool (RoB2) for evaluating research quality, with one trial (Agata et al., 2010) excluded due to a high risk (Figure. 4). Finally, I included 22 RCTs for data extraction. The PRISMA flow is shown in Figure. 5.

I classified the included 22 trails according to the surgical type. The settings of two dosages, number of participants, and outcomes were summarized in Table. 2.



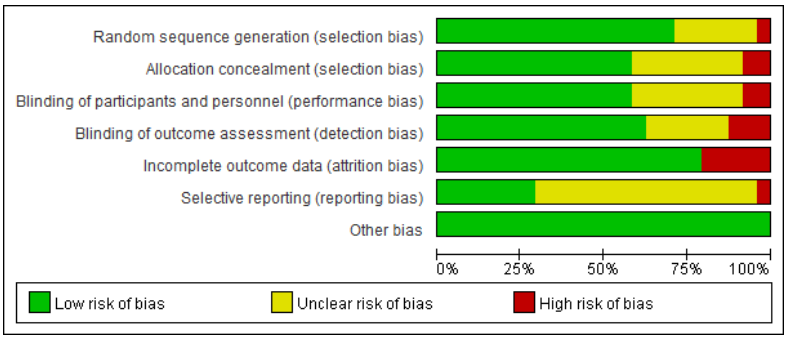


Fig. 4 Risk of bias of screened RCTs. Overall, the included trials showed relatively low a risk of bias in selection, performance, detection and attribution, except that the reporting bias was almost unclear. One trial (Agata 2010) was excluded for data extraction due to a high risk of bias.

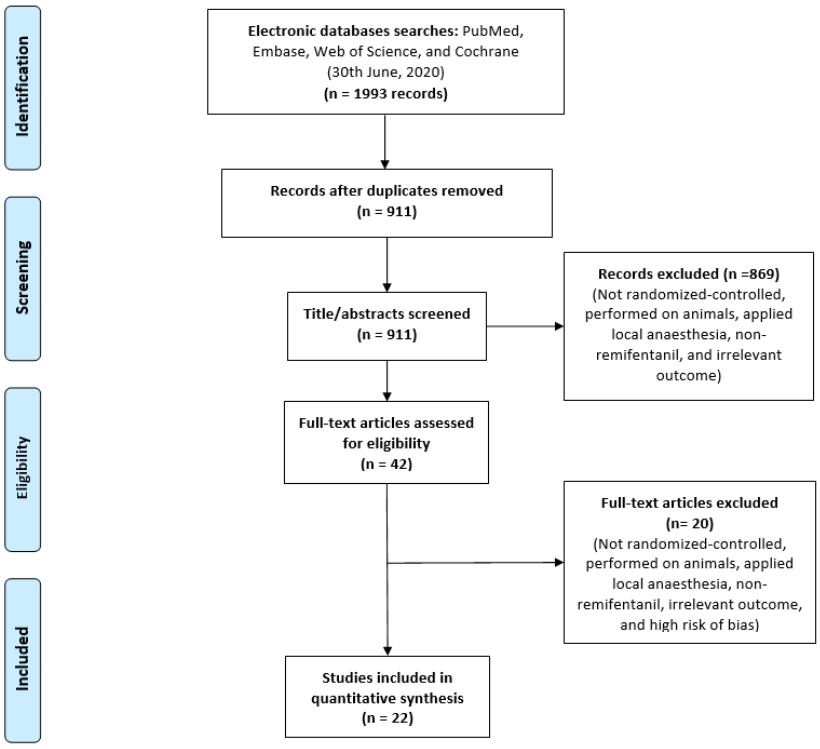


Fig. 5 The PRISMA flow of RCTs-inclusion process for investigating the influence of intraoperative remifentanil dosage on postoperative pain outcomes.

Data synthesis

It was impossible to complete a meta-analysis due to a mass of missing data of reported outcomes and precise p-values, with attempts to request the authors for raw data were limited by time. Also, one previous systematic review with similar search results (Albrecht et al., 2020) showed a high statistical heterogeneity (I^2 = 80%), this indicated a limited validity of meta-analysis for this topic. Therefore, I employed a "vote-counting" of the studies favoured direction of effect instead (Table. 2). This aimed at giving a more powerful analysis than narrative description only.

Interpretation of results

For the favours of results, "Comparable" represents low-dose and high-dose is not significant different; "Higher" represents high-dose remifentanil resulted in higher pain scores (and/ or cumulative postoperative analgesics consumption) than low-dose; "Lower" represents high-dose resulted in lower scores (and/ or cumulative postoperative analgesics consumption).

RESULTS

The results are also demonstrated through two sections corresponding to the two systematic reviews.

Section 1. Methods to detect intraoperative nociception during the surgery.

Nineteen methods were found and classified into seven categories based on the method used and/or the signal types. Signal types include sympathetic tone, parasympathetic tone, electroencephalography, combined signals, electromyogram, drug models, and neuroimaging. These are listed in Table. 1 in the order of popularity (parasympathetic tone was discussed following sympathetic tone since they are all based on automatic response).

In this section, I give a brief overview of the 7 categories including monitoring principle, tested accuracy and their limitations.

1 Sympathetic-tone based

Assessing autonomic activities can detect intraoperative nociception since noxious stimuli would increase sympathetic tone while decrease parasympathetic tone inversely. Based on the sympathetic response to nociception, there are 7 methods

developed for monitoring nociception intraoperatively that we will review briefly in this section.

1.1 Surgical Stress Index (Otherwise known as Surgical Pleth Index), also Autonomic Nervous System State Index

Principle of work: Based on the responses of photoplethysmograph (PPG) waveform to noxious stimulations, Huiku et al. (2007) developed Surgical Stress Index (SSI), later named as Surgical Pleth Index (SPI) (GE Healthcare Company, Helsinki Finland). SPI was calculated through a designed unique algorithm by normalizing nociception-related physiological variables, the wave amplitude of PPG (PPGA) and heart-beat interval. A single index of SPI ranges from 0-100, with a low scale represents low nociceptive level and vice versa. SPI is able to quantify the physiological, hemodynamic and sympathetic stress response changed by nociception (Ahonen et al., 2007; Ilies et al., 2012).

Autonomic Nervous System State Index (ANSSI) uses same variables of PPGA and heart-beat interval like SPI, but is not normalized into averaging and learning algorithms. ANSSI has been used as a substitute to SPI since SPI is only commercially available with undisclosed normalisation process (Colombo et al., 2017). ANSSI is theoretically functioning similar to SPI in reflecting intraoperative NAN balance (Paloheimo et al., 2010; Colombo et al., 2017).

Performance: SPI is more specific and accurate in detecting noxious stimulation than conventional signals (e.g., HR or BP) (Struys et al., 2007; Wennervirta et al., 2008). In a study by Funcke et al. (2017) under propofol-remifentanil anaesthesia, SPI demonstrated a sensitivity=74.2% and specificity=86.4% in detecting nociception. Wennervirta et al. (2008) and Paloheimo et al. (2010) reported that SPI enabled the differentiation of different analgesic levels (tested by inducing different effect-site analgesic concentrations). SPI presented a small reactivity level in children (Harju et al., 2016; Ledowski et al., 2017), but Song et al. (2017) described that SPI failed to grade analgesic levels in paediatric surgery, indicating a potential but insufficient sensitivity of SPI for monitoring children.

Limitations: A large inter-individual was identified, impairing the defining of optimal values and detecting sensitivity (Harju et al., 2016; Heyse et al., 2014). Differences

among analgesia agents and anaesthetics lead to varied pharmacodynamic interactions, resulting in inconsistent sensitivity and specificity (Heyse et al., 2014). Other possible confounding factors influencing autonomic reactions (e.g. insufficient hypnosis) should always be questioned for SPI's monitoring accuracy. Ilies et al. (2012) discovered the significant influence of intraoperative positioning on SPI values. Also, difference in pulse oximetry probes sites, such as earlobe or finger, could affect monitoring interpretation (Ahonen et al., 2007).

1.2 Pupillometry：Pupillary Reflex Dilatation and Pupillary Pain Index

Principle of work: Pupillary Reflex Dilatation (PRD) measures nociception as altering noxious stimuli evoke PRD and increase pupillary diameter (Larson et al., 2015). Due to the size constriction induced by anaesthesia effects, pupil size and other variables of the reflex, such as latency, duration, maximum amplitude, percentage variation in size random size fluctuations and dilation velocity, were combined to assess the nociception response (Abad-Torrent et al., 2017). A portable infrared pupilometer (designed by AlgiScan; IDMED, Marseille, France) allows the measurement of PRD by sending an infrared light to eye and collecting the reflected light from the iris by a sensor (Vide et al., 2018). The degree of PRD after experiencing an induced electric stimulation was normalized into the Pupillary Pain Index (PPI), ranging from 1 to 10. A PPI score of 2-3 refers to the optimal analgesia state (Vide et al., 2018).

Performance: PRD can reflect nociception more rapidly than conventional signals with shorter latency since without dependence on activating sympathetic nervous system (Larson et al., 2015). PRD reflects the nociceptive intensity proportionally (Sabourdin et al., 2017), an increase of size more than 6 % is indicative to a significant nociception (Abad-Torrent et al., 2016). Also, Huybrechts et al. (2006) reported that PRD higher than 1 mm may be highly predictive to insufficient. Funcke et al. (2017) reported a high sensitivity=93.9% and specificity=100% of PRD in detecting nociception, although with a poor ability [P(k)=0.67] for predicting hemodynamic or movement response. In children, Constant et al. (2006) claimed that PRD increased significantly (+200%) 60 s post stimulation, more sensitive than mean HR and BP.

Limitations: Age is an important factor influencing pupil size, reported that a decrease of around 0.4 mm occurs every decade after 16-yr-old (Larson et al., 2015). Also, PRD

is sensitive to medication interactions. Some antiemetics or drugs (e.g., ketamine) may affect N-methyl-d-aspartate receptor antagonism, resulting in decreased baseline diameter or PRD response (Vide et al., 2018; Merlin and Larson, 2003). Moreover, PRD requires access to opened eyes, leading to the inconvenience of continuous monitoring (Larson et al., 2015).

1.3 Skin Conductance

Principle of work: Skin conductance [(SC), MedStorm Innovation AS Company, Oslo, Norway] is a monitoring signal developed based on the emotional sweating responding to stress. This autonomic response can induce variations in electro-galvanic skin properties, including the number of skin conductance fluctuations per second (NSCF) (n) and their amplitude (Storm et al., 2005), becoming indicative to nociception.

Performance: Storm et al. (2005) claimed that using SC or NSCF alone was reliable for stress detecting. They studied the monitored patterns and reported that the combination of SC and NFSC values might discriminate the cause of stress (insufficient hypnosis or insufficient analgesia). Gjerstad et al. (2007) found NSCF could detect noxious stimulation under different remifentanil effect-site concentrations. However, these studies did not present the sensitivity and specificity to nociception. Conversely, Ledowski et al. (2010) and Sabourdin et al. (2013) reported that NSCF failed to significantly change in terms of varied analgesia levels under fentanyl or remifentanil analgesia, concluding that NSCF may not be valid for intraoperative nociception monitoring. But this negative finding was doubted by Storm et al. (2013) with not using pre-set values.

Limitations: The accuracy of SC monitoring is still controversial. Other limitations remain unclear, more studies on the SC reliability are required.

1.4 Cardiovascular depth of analgesia (CARDEAN) index

Principle of work: The cardiovascular depth of analgesia [(CARDEAN), (Alpha-2 Ltd., France)] reflects nociception by presenting adrenergic effects from the brain stem. CARDEAN linked inhibited cardiac baroreflex, activated somato-sympathetic reflex and nociception together. A designed algorithm measures beat-by-beat cardiac

parameters: systolic blood pressure (SBP) and HR, generating a CARDEAN index ranges from 0-100 (Rossi et al., 2012; Martonez et al., 2010).

Performance: CARDEAN reflects subtle variations much more sensitively than the regular monitoring of individual HR and SBP (Rossi et al., 2012). Martinez et al. (2010) first evaluated CARDEAN by testing its probability in guiding propofol-alfentanil anaesthesia. They reported a 51% reduction of nociception-induced movement events when hypnosis was sufficient (BIS＜ 60), suggesting the potential of CARDEAN for detecting inadequate analgesia in unconsciousness. Rossi et al., (2012) discovered a correlation between CARDEAN and nociception-related circulatory response (tachycardia and hypertension, P(k)=0.81). Also, they confirmed the cut-off value of CARDEAN= 60 (Sensitivity=70%, Specificity=88.2%) when BIS＜ 60 (Rossi et al., 2012).

Limitations: CARDEAN presents a delay of displaying real-time analgesia state since sympathetic nervous system requires a reacting duration to reflect perceived nociception (Martinez et al., 2010). Also, the nociception detection ability of CARDEAN under grossly inadequate analgesia is limited, only 80-85% response was detected by CARDEAN earlier before observable signs appeared (Rossi et al., 2012). Aging may alter vagal and baro-deafferentation functions and influence CARDEAN accuracy (Rossi et al., 2012). Overall, relevant assessments of CARDEAN reported are limited for patients in American Society of Anaesthesiologists (ASA) class 1-2, the reliability for ASA 3-4 requires further studies (Rossi et al., 2012).

1.5 Analgoscore

Principle of work: Analgoscore is an index based on mean arterial pressure (MAP) and HR response to induced noxious stimulations. An offset percentage between the targeted and measured MAP and HR values is calculated as Analgoscore through fuzzy logic algorithms. Analgoscore generated every minute repeatedly to reflect the NAN balance. Analgoscore ranges from -9 to 9 in increments of 1. A score closer to -9 represents more analgesia, while 9 representing less (Hemmerling et al., 2007).

Performance: Hemmerling et al., (2007) evaluated Analgoscore by testing its utility of guiding a closed-loop remifentanil administration. The authors found that Analgoscore monitoring contributed to the more rapid and accurate modification of remifentanil dose. Finally, they reported a steadier MAP and HR value, with fewer unwanted variations (10%) and longer controlled time (91%-99% of total time). This study indicated the potential reliability of Analgoscore for NAN balance monitoring (Hemmerling et al., 2007).

Limitations: Only one published study reported Analgoscore and the sample size was small, leaving plenty of unsolved questions and unclear limitations. The influence of surgical and participant factors on determining the target value of MAP and HR is questioned. More studies under different nociception intensities are needed.

1.6 Nociceptive Response (NR) index

Principle of work: Nociceptive Response (NR) index is based on that nociception can increase HR and SBP while decrease perfusion index. Hirose et al. (2018) combined HR, SBP, and perfusion index via designed equations and generate a single NR value. It enables both real-time and averaged intraoperative NAN balance monitoring without special equipment required (Hirose et al., 2018).

Performance and limitations: Only one study reported NR monitoring, and the accuracy of detection remains untested. Also, the validity under different noxious stimulations more than skin incision, or different anaesthetics settings remains unclear. Moreover, Hirose et al. (2018) claimed vasopressors or vasodilators could influence NR variables. This indicates NR is unreliable to monitor patients taking high doses of vasoactive agents (common for patients with severe cardiovascular conditions).

1.7 Arterial stiffness (K) index

Principle of work: Arterial stiffness (K) level was calculated by Yanabe et al. (2018) through measuring circulatory changes responding to noxious stress. K combines circulatory parameters arterial pressure and PPGA with time to be related to NAN balance.

Performance: Yanabe et al. (2018) evaluated K and reported a non-proportional positive relationship between the normalised K values and stimulus intensities. Meanwhile, K responded to graded analgesics dosage significantly, suggesting the potential of K for NAN balance monitoring.

Limitations: K was only studied by Yanabe et al. (2018) with limited settings: their sample size was not big enough to analyse the confounding factors from patients (e.g. age, gender, body-weight) which could influence K; a relative wide inter-individual variability existed, which may impair the determination of optimal values. Further investigations on detection accuracy are required.

2 Parasympathetic-tone based

There is only one method in literature that is based on assessing parasympathetic tone which is called Analgesia Nociception Index.

Analgesia Nociception Index

Principle of work: The Analgesia Nociception Index [(ANI), Mdoloris Medical Systems Company, Loos, France] assesses cardiac response to nociception by recording heart rate variability (HRV) from high-frequency (0.15-0.40 Hz) spectral power (Ledowski et al., 2014). The derived HRV is normalized into an ANI score ranging between 0 and 100. A high score represents a higher level of parasympathetic tone, low stress, and adequate anti-nociception, and vice versa (De Jonckheere et al., 2012). ANI can show instantaneous or average values derived from past 2-4 mins (Weber et al., 2018; Sabourdin et al., 2013).

Performance: ANI is reportedly significant for diagnosing intraoperative nociception for both adults and children. ANI showed better sensitivity and specificity compared with conventional signals (Julien-Marsollier et al., 2018). Funcke et al. (2017) reported that ANI showed a sensitivity=87.9% and specificity=98.5% in detecting nociception. Sabourdin et al. (2013) and Migeon et al. (2013) also claimed that ANI modified significantly according to the induced different noxious stimulation intensities and analgesics levels in children.

Limitations: many non-nociceptive disruptive factors may influence HRV values of ANI detecting. The confounders include patient positioning, drugs or pathology affecting autonomic activity, or any known disturbances to ECG (Weber et al., 2018; Sabourdin et al., 2013). Also, the pharmacodynamic profiles may limit ANI interpretation. For instance, some co-acting anaesthesia agents (e.g. ketamine) showing sympathomimetic properties may alter the assessed parasympathetic tone (Sabourdin et al., 2013; Boselli et al., 2016).

3 Electroencephalogram-based

Electroencephalogram (EEG)-based devices are widely used for intraoperative anaesthesia monitoring, especially for maintaining hypnosis levels (Mathews et al., 2012). There are five multi-variable EEG-derived methods designed targeting at monitoring analgesia.

3.1 Composite Variability Index

Principle of work: Mathews et al. (2012) developed the Composite Variability Index [(CVI), Covidien, Mansfield Company, MA, USA] by combining sBIS, facial electromyogram variability (sEMG) and BIS linearly. A proprietary algorithm processed the variables, generating a CVI score between 0-10 to grade the nociceptive state. A higher CVI score represents a higher nociceptive level (Mathews et al., 2012).

Performance: Mathews et al. (2012) first reported that CVI responded earlier than HR in detecting intraoperative somatic events. Then, Sahinovic et al. (2014) claimed CVI could detect somatic response to noxious stimulations. However, more studies showed negative results. Von-dincklage et al. (2012) reported a poor CVI ability to predict nociception-induced responses [P(k)=0.41-0.58]. Ellerkmann et al. (2013), Lopes-pimentel et al. (2017) and Heyse et al. (2014) reported a significant large inter-individual variability in CVI, indicating CVI value alone may be unreliable for predicting NAN balance.

Limitations: Except for the main problem of uncertain detection validity, CVI was easily affected by electromyography activity and failed to discriminate the non-responsiveness movements (Von-dincklage et al., 2012). Sahinovic et al. (2014) also reported CVI was more affected by hypnotic drugs than by opioids. This

pharmacodynamics reaction limits CVI utility. Other limitations remain unclear and require more studies.

3.2 qNOX index

Principle of work: qNOX index (Quantium Medical Company, Barcelona, Spain) was generated by combining nociceptive responses of various EEG frequency bands. qNOX ranges from 0 to 99; a higher score represents a higher pain level.

Performance: Jensen et al. (2014) described that qNOX as potentially useful for monitoring nociception, since qNOX enabled the discrimination of movements responding to noxious or non-noxious stimuli during general anaesthesia. However, the reliability of monitoring was doubted by Ledowski and Schmitz-rode (2020). They assessed the probability of qNOX predicting immediate postoperative pain, reported that there was no significant correlation (AUC = 0.501). Considering that this predictive correlation was ever found in ANI, SPI and PRD (Ledowski et al., 2019; Boselli et al., 2014; Jakuscheit et al., 2017), Ledowski and Schmitz-rode (2020) doubted the previously claimed potential of qNOX. Also, since Jensen et al. (2014) stated that qNOX might be significantly affected by hypnosis level and electromyogram (EMG) activity, Ledowski and Schmitz-rode (2020) recommended qNOX to be a secondary monitor of anaesthesia level rather than of analgesia.

Overall, qNOX is currently little studied, requiring further investigations on its reliability and limitations.

3.3 Response Entropy and State Entropy difference (RE-SE) index

Principle of work: State Entropy (SE) represents EEG-dominant frequency spectrum reflecting arousal state. Response Entropy (RE) represents both EEG- and EMG-dominant parts. Their difference RE-SE can demonstrate the facial EMG activity, which is one potential indicator of nociceptive stimuli (Aho et al., 2008).

Performance: Aho et al. (2008) evaluated the reliability of RE-SE and reported that RE-SE increased significantly during strong stimuli. However, it failed to be long-lasting due to the soon increased SE value following RE-SE response. This increase was explained by the lifted EMG activity in response to stimulation generated from brain

stem, contaminating signals even when hypnosis was sufficient. Also, Takamatsu et al. (2006) found RE-SE showed low accuracy [P(k)＜0.8] in discriminating nociceptive levels. Therefore, concluded by these authors, RE-SE difference is not a reliable value for monitoring nociception intraoperatively.

3.4 A-line Autoregressive Index

Principle of work: A-line Autoregressive Index (AAI) (measured with A-Line AEP electrodes and A-Line monitor) was generated from the middle-latency auditory evoked potentials (MLAEPs). Bonhomme et al. (2006) found that an increase of AAI was linked to noxious stimuli when hypnosis was sufficient. However, the mechanism was unclear.

Performance and limitations: Researchers reported that AAI enabled detecting nociception intraoperatively when using BIS as guidance for maintaining a constant hypnotic level (Bonhomme et al., 2006). However, Ekman et al. (2007) detected an influence of neuromuscular blocking drugs (NMBD) on AAI response to noxious stimuli. This pharmacodynamics effect may impair detecting accuracy, limiting its utility. Monitoring accuracy and other limitations require further study.

3.5 Somatosensory evoked potentials

Principle of work: Somatosensory evoked potentials (SEP) is an EEG-derived signal. Since pain is one sensory perception could activate somatosensory cortex, SEP is potential for nociception monitoring (Zanatta et al., 2011). Zanatta et al. (2011) found the amplitude of SEP always increased after intraoperative pain stimulations.

Performance: Zanatta et al. (2011) evaluated SEP during cardiac surgery, both short and middle-latency SEP showed an increased amplitude and decreased latency, responding to noxious stimulations sensitively (of 84% patients).

Limitations: The utility of SEP for intraoperative analgesia monitoring is little studied. Only a correlation between SEP and intraoperative nociception was proved, lacking investigations on analgesia level grading. Zanatta et al. (2011) reported low sensitivity of SEP to detect low-intensity noxious stimulation. Also, pain under insufficient hypnosis may induce movement artefacts, influencing interpretation. Moreover,

researchers claimed that the difference in electrode montages might affect monitoring results (Zanatta et al., 2011).

4 Combined indices

There are several indices combine different types of nociception-related signals. The combined indices might mitigate the shortcomings of each single signal, improving detection accuracy.

4.1 Nociception Level index

Principle of work: The Nociception Level index (NoL) combines five parameters: HR, high-frequency HRV, PPGA, SC, NSCF and their time derivatives. PMD100™ or PMD 200™ equipment (Medasense Biometrics Ltd., Ramat Yishai, Israel) monitor these parameters and computes the NoL index. NoL scales between 0-100 to represent nociception level, a higher index indicates more nociception.

Performance: Since NoL covers both sympathetic and parasympathetic parameters, it was supposed to be more accurate and reliable than the individual signals for detecting nociception (Ben-Israel et al., 2013). Treister et al. (2012) first evaluated this multi-parameter method by inducing four categories of pain (high, medium, low, and no pain). They reported that the linear combination of these five parameters discriminated varied pain intensities significantly, while individual parameter failed to achieve. Ben-israel et al. (2013) confirmed this finding and developed NoL through selected regression techniques using same parameters. NoL also showed a superior ability in predicting nociception level (AUC=0.97) than individual parameters (AUC=0.56-0.74) intraoperatively. Several studies evaluated NoL by inducing different level of noxious stimuli with various remifentanil concentration during general anaesthesia. Among these studies, Martini et al. (2015), Renaud-roy et al. (2019) and Edry et al. (2016) reported the superiority of NoL in discriminating noxious versus non-noxious condition. Also, NoL graded nociception level more accurately than HR, MAP, PPGA and BP [AUC of NoL=0.9, Sensitivity=88%, Specificity=79.1% (Renaud-roy et al., 2019); AUC of NoL=0.93, Sensitivity=87%, Specificity=87% (Edry et al., 2016)]. Moreover, NoL was not influenced by remifentanil- concentration induced hemodynamic effects, indicating its better accuracy and reliability (Martini et al., 2015). Ben-Israel et al. (2013) reported a sensitivity=89%, specificity=92% under isoflurane-

or sevoflurane-remifentanil or fentanyl anaesthesia, while Martini et al. (2015) reported a sensitivity=73%, specificity=80% under propofol-remifentanil anaesthesia.

Limitations: The limitations of NoL were less reported. Bollag et al. (2018) recommended that an accurate interpretation of the nociceptive state requires validating the cut-off value according to surgical settings. Drugs affecting hemodynamic parameters (e.g. intravenous phenylephrine on HR and MAP) may influence the accurate interpretation of NoL (Raft et al., 2019).

4.2 Response Index of Nociception

Principle of work: Rantanen et al. (2006) designed a Clinical Signs-Stimulus-Antinociception (CSSA) score for assessing NAN balance. However, the CSSA failed to provide continuous monitoring. Based on the CSSA, the same authors developed the Response Index of Nociception (RN), aiming at monitoring continuously during surgery. They selected the most effective indicators of CSSA, including HRV, PPG, RE and SE. These variables were combined with a designed algorithm and generated RN. RN scaled between 0-100, a higher score represents lower analgesia.

Performance: Rantanen et al., 2006 evaluated RN during general anaesthesia by inducing skin incisions and comparing acquired RN with CSSA. They reported that the probability of RN predicting CSSA was not high [P(k)=0.78] but acceptable, suggesting the potential of RN for monitoring NAN. Saren-koivuniemi et al., (2011) confirmed RN was able to detect different noxious events and predict movement response, with a maximum accuracy of 79%, sensitivity and specificity of 63%.

Limitations: The accuracy of CSSA is uncertain. Therefore, using CSSA as a reference for testing RN performance is less reliable. RN is still little-studied, further validations under different surgical settings are required.

4.3 Steady-state index during general Anaesthesia

Principle of work: Steady-state index during general Anaesthesia (STAN) is a multi-variable index designed by Castro et al. (2017). It analyses the wavelet of nociception-related signals, including BIS, front EMG, the HR of ECG, BP and PPG amplitude, aiming at reflecting NAN balance intraoperatively.

Performance: Castro et al. (2017) evaluated STAN responses to the induced noxious stimuli under different analgesic levels. Significant correlations between STAN and either noxious stimuli or analgesics doses were reported, suggesting STAN's reliability of NAN balance monitoring (Castro et al., 2017).

Limitations: STAN is still little studied for accuracy and limitations. Castro et al. (2017) stated an inter-individual variation of the optimum steady-state for analgesia level determination, requiring more monitoring testing under different settings.

5 Electromyogram-based

There is only one method monitoring based on electromyogram response to nociception.

Nociceptive Flexion Reflex Threshold, also RIII Threshold

Principle of work: Noxious stimuli can induce spinal withdrawal reflex through nociceptive afferents. Therefore, the threshold of withdrawal reflex could indicate nociceptive thresholds (Von-dincklage et al., 2008). EMG-derived Nociceptive Flexion Reflex Threshold (NFRT) and RIII threshold (Dolosys GmbH, Berlin, Germany) are potential for nociception monitoring.

Performance: Von-dincklage et al. (2008) evaluated the RIII threshold and claimed that personal RIII threshold might estimate the nociceptive response. Von-dincklage et al. (2010 and 2012) then reported that NFRT and RIII enabled prediction of movement and HR response to noxious stimuli [P(k)= 0.68-0.77 and 0.77-0.84, respectively]. Also, Jakuscheit et al. (2017) found NFRT was predictive to the signs of over-analgesia and under-analgesia intraoperatively, indicating the potential reliability of NFRT for NAN monitoring.

Limitations: Due to both hypnosis and analgesia influence the reflex significantly, sufficient hypnosis should always be maintained to improve the detecting specificity to nociception (Von-dincklage et al., 2010). Researchers also detected a large inter-individual variability of the threshold, suggesting that personalized threshold are required for reference (Von-dincklage et al., 2008). The required personalized

parameters may limit the NFRT clinical utility. Also, the influence of pharmacodynamics on reflex are significant but remains unstudied.

6 Drug interaction models

Drug interaction parameter (U), also Noxious Stimulus Response Index (NSRI)

Principle of work: Based on pharmacodynamic interactions, different drug concentrations with different drug combinations can induce varying anaesthsia effects. Drug interaction models: the drug interaction parameter (U) and the Noxious Stimulus Response Index (NSRI), are potential for assessing NAN balance in terms of real-time calculated analgesia potency during the surgery. U measures sevoflurane-remifentanil drug interaction (Heyse et al., 2012), and NSRI measures propofol-remifentanil combination (Hannivoort et al., 2013).

Performance: Hannivoort et al. (2013) evaluated the prediction probability of U and NSRI responding to different noxious stimuli under general anaesthesia. They reported that both U and NSRI showed significantly higher ability (96-98% and 94-96%, respectively) compared to BIS, CVI and SPI, suggesting the potential of drug models for monitoring nociception.

Limitations: The pharmacodynamic models generated the index by combining both hypnotics and analgesics concentration values, therefore, interference from insufficient hypnosis on index interpretation should be noticed (Heyse et al., 2012).

7 Neuroimaging

Nociception could activate the brain network to be detected by neuroimaging techniques. There is only one method of neuroimaging presents a potential for continuous and non-invasive intraoperative monitoring.

Functional Near-Infrared Spectroscopy

Principle of work: Functional Near-Infrared Spectroscopy (fNIRS) detects pain by measuring cerebral hemodynamic response to perceived-nociception (Becerra et al., 2016). The activated cortical area could show increased blood flow and oxygen delivery, changing the volume of oxygenated, deoxygenated, and total hemoglobin, reflected through fNIRS (Kussman et al., 2016).

Performance: Gelinas et al. (2010) first evaluated fNIRS during general anaesthesia and found that fNIRS responded to the induced nociception with an increase of regional cerebral oxygenation. Becerra et al. (2016) recorded continuous NIRS data and reported that NIRS reflected pain-induced brain activation sensitively. Kussman et al. (2016) found the fNIRS patterns of nociception-perception during general anaesthesia mirrored that in healthy awake participants. Mukaihara et al. (2017) also indicated the ability of fNIRS to evaluate the depth of analgesia for nociception monitoring.

Limitations: Mukaihara et al., (2017) found that fNIRS seems to be significantly affected by perioperative medications (e.g. intraoperative paravertebral block and premedication), limiting its clinical utility. The MAP, BP, and HR changes resulted from non-noxious events may influence fNIRS interpretation as well, impairing the specificity to nociception.

Summary of main results

The results showed that, first, among these 19 methods of 7 signals, the most popular methods are SPI, PRD, and ANI, which are all based on measuring autonomic responses to nociception. However, all this three methods presented limitations with multiple confounding factors. They all have design-related shortcomings. Moreover, they are affected by surgical settings significantly, including intraoperative positioning, and pharmacodynamics profiles of anaesthetics and analgesics interactions. PRD ever presented the highest sensitivity=93.9 and specificity=100%, but only under propofol sedation. Most of other methods are little studied, without specific investigations on detecting accuracy and limitations. Overall, there is no methods showing both 99% sensitivity and specificity, and no method is developed based on human bio-fluids.

Table 1. Monitoring principles, limitations and maximum reported accuracy of intraoperatively-used nociception detection methods							
Name of method	**Monitored signals**	**Range of value**	**Optimal threshold**	**Design principle**	**Limitations**	**Maximum accuracy**	**Number of studies**
1 Sympathetic tone-based							
Surgical Stress Index (SSI), otherwise known as Surgical Pleth Index (SPI), Autonomic Nervous System Index (ANSSI)	Plethysmograph (PPG) waveform	0-100 (dimensionless, higher value indicates higher stress).	20-50	SPI (SSI): Measures and combines heart-beat interval and the photoplethysmographic waveform amplitude (PPGA) into a normalized score through a unique algorithm. ANSSI: measures and combines the changes of PPGA and heart-beat interval into a value, without normalizing process.	1. Age-induced large inter-individual variability. 2. Influenced by many confounding factors: e.g., intraoperative positioning, pharmacodynamics, and location of measurement. 3. May be insufficiently sensitive for monitoring children.	Sensitivity =74.2%, Specificity =86.4% in detecting noxious stimulations (Funcke et al. 2017).	44
Pupillometry: Pupillary Reflex Dilation (PDR) otherwise known as Pupillary Pain Index (PPI)	Absolute or variations of diameter	Not defined	Size increase of pupil $\leqslant$ 6%, or a PPI score 2-3	PRD: An infrared portable pupillometry measures every 30 milliseconds continuously with an accuracy of 0.05 mm (Funcke et al., 2017). PPI: measured by video pupillometry, with a camera recording the degree of PRD after an automatically increased electric stimulation.	1. Requires access to opened eyes may limit the convenience of continuous monitoring 2. Influenced by many cofounding factors: e.g., anaesthesia effects may constrict pupil size, aging decreases baseline pupil size, and altered sensitively to medication interaction.	Sensitivity =93.9%, Specificity =100% in detecting noxious stimulations (Funcke et al. 2017).	25
Skin Conductance (SC)	Number of skin conductance fluctuations per second (NSCF) (n) and their amplitude	Not defined	NFSC $\leqslant$ 0.2	NCSF rapidly increases during stimulations and decreases after stimulations removed, enables real-time monitoring of nociceptive status.	1. NFSC may be more limited to detect high-level nociception. 2. Controversial reliability among studies.	Not specified	9

Cardiovascular depth of analgesia (CARDEAN) index	Beat-by-beat systolic blood pressure (SBP) and heart rate (HR)	0-100 (dimensionless)	60	A rise of SBP amplitude exceeding the setting threshold and lasting for 10-20s could start the processing of CARDEAN to present nociception, demonstrating discontinuous values.	1. Real-time nociception displaying is influenced by the delay of rising BP and BP-HR interaction. 2. A prediction delay to observable signs exists, which only enables the detecting of not grossly inadequate anti-nociception. 3. Aging-induced vagal and baro-deafferentation function alteration may affect monitoring accuracy. 4. Lack of study for patients in ASA 3-4.	Sensitivity =70%, Specificity =88.2% in detecting nociception-related circulatory response. (Rossi et al., 2012).	3
Analgoscore	Mean arterial pressure (MAP), heart rate (HR)	-9 to 9 (in increments of 1, closer to -9 represents more analgesia, closer to 9 represents less analgesia)	-3 to + 3	The designed fuzzy logic algorithms calculate the offset percentage between the targeted and measured MAP and HR variables, generating the Analgoscore.	1. The targeted value index calculation may be influenced by the surgery type and inter-individual variability. 2. Little studied for accuracy and limitations.	Not specified	1
Nociceptive Response (NR) value	HR, systolic blood pressure (SBP), and perfusion index	0-1	≤ 0.70	The HR, SBP, and perfusion index are combined by an equation into a single value, presenting both real-time and averaged nociceptive conditions.	1. Influence by vasopressors or vasodilators, limiting application in patients receiving high doses of vasoactive agents. 2. Doubtful validity for noxious stimulations except skin incision. 3. Unclear sensitivity and specificity to nociception.	Not specified	1
Arterial stiffness (K) index	Arterial pressure, PPGA	Not defined	Not defined	Measuring and combining the value of arterial pressure and PPGA into a normalized arterial stiffness (K) value, reflecting nociceptive intensity	1. Little studied, the confounding factors from patients (e.g. age, gender, body weight) can influence K were not assessed.	Not specified	1

				in a non-proportionally changed form.	2. A relative wide inter-individual variability exists, may impair optimal value defining. 3. The detection accuracy remains unclear.		
2 Parasympathetic tone-based							
Analgesia Nociception Index (ANI)	Heart rate variability (HRV, 0.15-0.40 Hz)	0-100 (dimensionless, higher score represents lower parasympathetic activity level, higher analgesia).	50-70	Measuring HRV through a designed ECG and showing Instantaneous value or one averaged value of past 2 or 4 min.	1. Limited by many confounding factors, e.g., positioning, cardiac-related drugs and devices, and pharmacodynamics profiles.	Sensitivity =87.9%, Specificity =98.5% in detecting noxious stimulations (Funcke et al. 2017).	33
3 Electroencephalography-based							
Composite Variability Index (CVI)	The variation of bispectral index (sBIS) and the variation of electromyogram (sEMG)	0-10 (higher score represents the higher nociceptive level).	Not defined	Combining sBIS and sEMG with BIS through a designed algorithm to indicate nociceptive responses.	1. Controversial reliability: poor ability in discriminating non-responsiveness responses; more affected by hypnotic drugs. 2. Significant large inter-individual variability impairs accurate interpretation. 3. Affected by electromyography activity.	Prediction probability for nociceptive responses = 0.41-0.58 (Von-dincklage et al., 2012).	8
qNOX index	Electroencephalography(EEG)	0-99 (dimensionless, higher index indicates higher nociception level)	Not defined	Combining different frequency bands of EEG and generating index through an Adaptive Neuro Fuzzy Inference System (ANFIS) for continuous monitoring.	1. Little studied, the nociception detection benefit is controversial among studies 2. More likely a monitor for hypnotic status.	Not specified	4

Response Entropy and State Entropy difference (RE-SE)	Entropy RE and SE	Not defined	Not defined	High-level noxious stimuli can evoke a transient increase of RE-SE difference.	1. Poor ability in discriminating nociceptive levels. 2. Not a long-lasting indicator to nociception due to electromyogram contamination.	Prediction probability for discriminating nociceptive levels $<$ 0.8 (Takamatsu et al., 2006)	2
A-Line Autoregressive Index (AAI)	middle-latency auditory evoked potentials (MLAEPs)	Not defined	Not defined	AAI increases in response to noxious stimuli when hypnosis is sufficient, enabled nociception detection under BIS hypnotic guidance.	1. Neuromuscular blocking drugs affect AAI response and impair detecting accuracy. 2. Little studied, unclear accuracy and other limitations.	Not specified	2
Somatosensory Evoked Potentials (SEP)	The amplitude and latency of the cortical SEP	Not defined	Not defined.	Comparing real-time amplitude and latency of the cortical SEP with their baseline values to indicate nociceptive response.	1. Insufficient hypnosis induced movement artefacts to pain may influence monitoring. 2. May show low sensitivity in detecting low intensity noxious stimulation. 3. Little studied, limitations, such as effects of electrode montage, remain unclear.	Sensitivity= 84% in detecting patients with induced noxious stimulations (Zanatta et al., 2011).	2
4 Combination indices							
Nociception level index (NoL)	HR, high-frequency HRV, PPGA, SC and NSCF, and their time derivatives	0-100 (dimensionless, higher index indicates higher nociception level)	10-20	Combining nociception-related signals into a single index with regression models to indicate nociception. (Ben-Israel et al., 2013).	1. The cut-off value and optimal range is not well-validated. 2. Influence of pharmacodynamics requires cautions.	Sensitivity = 89%, Specificity = 92% in detecting nociception (Ben-Israel et al., 2013)	15
Response index of Nociception (RN)	HRV, PPG, RE, RE-SE	0-100 (higher score represents less analgesia)	2.5	Combining nociception-related HRV, PPG, RE, RE-SE values into a single score to allow continuous nociception monitoring intraoperatively.	1. Little studied, requiring further validation for different surgical settings.	Accuracy for detecting noxious stimulations = 79% (Saren-koivuniemi et al., 2011)	2

Steady-state index during general Anaesthesia (STAN)	BIS, EMG, Electrocardiography (ECG), blood pressure (BP), PPG and CO2 curve	Not defined	Not defined.	Wavelet analysis of nociception-related signals, including BIS, EMG, ECG, BP, PPG and CO2 curve changes to reflect NAN balance.	1. Little studied, the accuracy to nociception detection are not assessed. 2. The optimum state for analgesia level determination was not defined.	Not specified	1
5 Electromyogram -based							
Nociceptive Flexion Reflex Threshold (NFRT)	electromyography	Not defined	According to personalized threshold	Noxious stimuli can induce withdrawal reflex as potential nociception indicators.	1. Hypnotic status influence reflex significantly. 2. Large inter-individual variability exist, requiring personalized threshold for reference. 3. Drug effects on reflex remain unclear.	Prediction probability for nociceptive responses: NFRT = 0.68-0.77; RIII threshold = 0.77-0.84 (Von-dincklage et al., 2010; Von-dincklage et al., 2012).	4
6 Drug interaction models							
Drug interaction parameter (U), Noxious Stimulus Response Index (NSRI)	Drug combinations	Not defined	Not defined	Drug interaction models reflect analgesia potency, generating a single index for predicting nociceptive levels.	1. Little studied 2. Measure both hypnotics and analgesics concentrations with limited specificity to nociception.	Prediction probability for noxious stimulations: U = 96-98%; NSRI = 94-96% (Hannivoort et al., 2013)	2
7 Neuroimaging							
Functional Near-Infrared Spectroscopy (fNIRS)	concentration of oxygenated, deoxygenated, and total haemoglobin	Not defined	Not defined	Perceived nociception increases oxygen delivery of brain, changing the concentration of oxygenated, deoxygenated, and total haemoglobin. This change can be continuously monitored through fNIRS during the surgery.	1. Significantly affected by perioperative medications. 2. The interpretation is influenced by MAP, BP, and HR response to non-noxious events.	Not specified	4

Section 2. The influence of intraoperative analgesic dosages (IAD) on intra- and post-operative pain.

A total of 1412 patients from 22 trails were included in this review. There are three types of patient-reported scales, including the Visual Analogue Scale (VAS), Numeric Rating Scale (NRS), and Children's hospital of eastern Ontario Pain Scale (CheOPS). A variety of postoperative intravenous analgesics were used among trials. The compared results between low-dose and high-dose remifentanil were shown at different postoperative time-points. A p-value < 0.05 was applied to represent a significant difference. Overall, in the comparison of the relatively lower dosage with the relatively higher dosage, more than half of these trails (n=12) ever reported high-dose results in either higher pain scores or higher cumulative postoperative analgesics consumption (Table. 2).

Postoperative pain scores

Among 22 trails, 12 trials reported high-dose were "comparable" compared to low-dose, 9 "higher" than low-dose, and 1 "lower".

Cumulative postoperative analgesics consumption

Among 22 trails, 10 trials reported high-dose were "comparable" compared to low-dose, 11 "higher" than low-dose, and 1 "lower".

Table 2. The vote counting table comparing the administration of low-dose and high-dose of remifentanil.

(The vote counting goes for the impact of low-dose and high-dose remifentanil on postoperative pain scores and postoperative analgesics consumption**.** P-value represents the difference of pain outcomes in high-dose versus low-dose; P < 0.05 indicates a significant difference.)

	Study (name and year of publication)	**Surgery type**	**Low-dose (**$\mu g \cdot kg^{-1} \cdot min^{-1}$**)** average total dose (μg)	**High-dose (**$\mu g \cdot kg^{-1} \cdot min^{-1}$**)** average total dose (μg)	**Participants (**low-dose; high-dose**)**	**Postoperative pain outcomes of high-dose**								**Favoured overall pain results of high-dose remifentanil** (compared to low-dose)
						Pain scores/ Cumulative postoperative analgesics consumption	**Postoperative time points (hours)**							
							0.5	**1**	**3**	**6**	**12**	**24**	**48**	
Abdominal surgery (n=10)														
1.	Guignard 2000	Open colorectal surgery	0.1 1656	0.25 with increments of 0.05 4992	25; 24	VAS score	*	*	√	√	*	*	*	Higher
						iv PCA morphine						√		Higher
2.	Joly 2005	Open colorectal surgery	0.05 900	0.4 4700	25; 25	VAS score			*	*	*	*	*	Comparable
						iv PCA morphine							√	Higher
3.	Kim 2013	laparoscopic ureteroneocystostomy	0.3 7890	0.9 23760	15; 15 (children)	Children's hospital of eastern Ontario Pain Scale (CheOPS) score		*	*	*	*	*	*	Comparable
						iv fentanyl						√	*	Higher
4.	Kim 2018	Gastrectomy	2 $ng \cdot mL^{-1}$ (TCI) 923	12 $ng \cdot mL^{-1}$ (TCI) 5267	40; 40	VAS score			*	*	*	*	*	Comparable
						iv PCA fentanyl		√	*	*	*	*	*	Higher
5.	Kong 2016	Laparoscopic cholecystectomy	0.1 406	0.3 1067	24; 25	VAS score	√	√	√	*	*	*	*	Higher
						iv PCA fentanyl			√	√	*	*	*	Higher
6.	Koo 2016	Pancreaticoduodenectomy	1 $ng \cdot mL^{-1}$ (TCI) 841	4 $ng \cdot mL^{-1}$ (TCI) 2708	27; 26	NRS score		*	*	*	*	*	*	Comparable
						iv PCA morphine		*	*	*	*	*	*	Comparable
7.	Lee 2013a	Laparoscopic urologic surgery	0.05 600	0.3 3400	30; 29	VAS score		√		√	√	√		Higher
						iv PCA morphine					√			Higher

8.	Lee 2018	Laparoscopic gastrectomy	0.05 924	0.3 5668	40; 39	VAS score		√		√	√	√		Higher
						iv PCA morphine						√		Higher
9.	Su 2020	laparoscopic cholecystectomy	0.1 632	0.3 1693	30; 30	VAS score	√		√	√	*	*		Higher
						iv PCA sufentanil	√		√	√	√	√		Higher
10.	Treskatsch 2014	Intra-abdominal surgery	0.1 1394	0.2 with increments of 0.05 3040	15; 17	NRS score		*	*	*				Comparable
						iv PCA morphine		*	*	*				Comparable
Gynaecological surgery (n=5)														
11.	An 2019	Laparoscopic hysterectomy	0.1 721	0.3 2228	30; 30	VAS score				*	*			Comparable
						iv PCA morphine				*	*			Comparable
12.	Choi 2015	Gynaecological surgery	0.05 376	0.3 2520	25; 25	NRS score		*		√		√		Higher
						iv PCA fentanyl							√	Higher
13.	Kwon 2009	Gynaecological surgery	1 ng·mL^{-1} (TCI) 381	3 ng·mL^{-1} (TCI) 1170	20; 20	VAS score				*	*	*	*	Comparable
						iv PCA morphine				*	*	*	*	Comparable
14.	Song 2014	laparoscopic gynaecologic surgery	0.1 1000	0.3 2980	25; 25	VAS score		*						Comparable
						iv PCA morphine						*		Comparable
15.	Lee 2013b	Laparoscopic hysterectomy	0.05 413	0.3 2513	28; 29	VAS score		√		√	√	*		Higher
						iv PCA morphine					√			Higher
Thyroid surgery (n=3)														
16.	Koo 2017	Thyroid surgery	1 ng·mL^{-1} (TCI) 321	1 ng·mL^{-1} (TCI) 1101	30; 31	NRS score		*		*	*	*	*	Comparable
						Not specified								Comparable
17.	Song 2011		0.05	0.2	28; 28	NRS score				*		*	√	Higher

		Thyroidectomy	422	1118		iv fentanyl, tramadol, acetaminophen						*	Comparable
18.	Zhang 2014	Thyroidectomy	0.2	1.2		VAS score	√	*	*			*		Lower
			1067	6222	29; 28	iv morphine infusion						√		Lower
Cardiac surgery (n=2)														
19.	Florkiewicz 2015	Coronary bypass grafting or heart valve surgery	0.1	0.3	43; 47	VAS score						*	*	Comparable
			1892	5248		iv PCA oxycodone				*	*	*	*	Comparable
20.	Richebe 2011	Coronary artery surgery	7 ng·mL^{-1} (TCI)	0.3	19; 19	VAS score				*	*	*	*	Comparable
			3661	5330		iv PCA morphine							*	Comparable
Breast surgery (n=2)														
21.	Kim 2014	Local excision of breast	5 ng·mL^{-1} (TCI)	10 ng·mL^{-1} (TCI)	63; 63	VAS score	*			*		*		Comparable
			1013	1894		iv PCA ketorolac	*			*		*		Comparable
22.	Shin 2010	Mastectomy	Propofol group: 1 ng·mL^{-1} (TCI)	Propofol group: 4 ng·mL^{-1} (TCI)	Propofol group: 50; 46 Sevoflurane group: 48; 42	VAS score	√	√		√	*	√		Higher
			762	2064		iv PCA morphine	√	√		√	√	*		Higher
			Sevoflurane group: 1 ng·mL^{-1} (TCI)	Sevoflurane group: 4 ng·mL^{-1} (TCI)										
			870	2071										

iv = intravenous; PCA = patient-controlled analgesia; TCI = target-controlled infusion; VAS = visual analogue scale; NRS = numeric rating scale; * P > 0.05 compared to low-dose; √ P < 0.05 compared to low-dose.

DISCUSSION

During the surgery, an appropriate detection of intraoperative nociception is important for controlling analgesics administration. However, the conventional method of nociception-monitoring, such as monitoring individual signal HR or BP, is found incompetent. This review therefore investigated all innovated methods to give a presentation of the development and limitations of this field.

Findings of this project

This review showed that many signals have been studied for their potential of monitoring. However, there are three main points suggesting the existing inadequacies. First, the available methods widely show design-related shortcomings, and are affected by surgical settings significantly. Therefore, their utility and detecting accuracy may be limited in certain type of surgeries or patients. This deficiency failed to satisfy the clinical expectation of exploring a flexible method to be highly inclusive for different surgical conditions.

Second, the ability of separating analgesia from sedation is always challenging but essential for the validation of nociception-monitoring. Many analgesics have sedative effects (Cowen et al., 2015), therefore, a high sensitivity and specificity to nociception is required to rule in noxious and rule out non-noxious responses. However, this ability is a common deficiency for the majority of these 19 methods. PRD is the method showing a reportedly maximum sensitivity and specificity in detecting noxious stimuli. However, this performance is limited to propofol sedation only. In considering of the overall working principle, performance, and limitations, NoL may be a superior method than the others although did not show the highest accuracy. NoL combines several type of signals to mitigate drawbacks of design, and performed well as significantly differentiated noxious and non-noxious stimuli (Martini et al., 2012; Edry et al., 2016). When compared to SPI and ANI, NoL presented to be more reliable in detecting noxious events (Edry et al., 2016; Stockle et al., 2018). Additionally, NoL succeed to mitigate influence by remifentanil concentration-induced hemodynamic effects (Martini et al., 2015), indicating a superior pharmacodynamics stability. The potential superiority of NoL suggests that investigating the multi-variable methods may be a future development trend.

Third, although most methods showed promising results for monitoring, however, the majority of them (e.g., Analgoscore, AAI, NFRT, drug models) were little-studied. Generally, only the correlation between the monitored value and intraoperative nociception was proved, lacking evaluations on the detection accuracy and potential limitations. Some methods, such as the EEG-derived, were always questioned as not predictable for nociception monitoring but for sedation monitoring (Seitsonen et al., 2005). Therefore, their clinical utility remains unclear. Overall, the methods failed to distinguish noxious intensities should be considered as clinically insignificant, since estimating nociception-level is key for the guidance of analgesic closed-loop load.

An appropriate monitoring of NAN is related to optimum IAD administration. In the exploration of the effect of IAD on intra-and post-operative pain, this review discovered the intraoperative influence based on two situations: 1) insufficient anti-nociception: anaesthetists increase IAD to decrease pain; 2) sufficient anti-nociception: there is no need to use analgesic, or increasing IAD do not influence intraoperative pain. However, due to the uncertain reliability of nociception-monitoring methods for proper reference, it is impossible to evaluate the precise IAD influence on unconscious patients. The postoperative influence was based on 22 RCTs and vote counting of their favoured effects. Although the higher intraoperative dose does not necessarily lead to the worse postoperative pain, a low-dose seems to be much safer. There is only one trial showed a controversial result as low-dose led to worse pain, it was explained as the high-dose induced a more persistent analgesic effect than low-dose (Zhang et al., 2014). Actually, this result may should not be taken into account in this review, since the setting of low-dose in this study is closer to the high-dose setting of the majority of other trails. Also, its high-dose setting is around 3-4 times higher than the high-dose of other studies. This difference of setting may increase the heterogeneity in this review, although it also indicated that a much higher dose than regular settings may result in inverse pain results, requiring further investigations.

Overall, the findings indicate that controlling IAD within a relatively low level can mitigate some potential postoperative pain conditions, and this control can be optimised by an appropriate method of monitoring intraoperative nociception. To date, there is no available method could satisfy this need.

Potential bias of results and review process

First, since the detecting methods were evaluated by different outcomes with varied statistic measures among studies, thus, a standardized comparison of their tested accuracy are not achievable. The influence of intraoperative opioid concentration on detecting accuracy was also found significant, therefore, the interpretations of reliability may be inconsistent among different settings.

Second, all retrieved RCTs of IAD effects are based on acute pain conditions within 48 postoperative hours, the chronic pain outcomes were not evaluated. Also, only a specific type of analgesic was evaluated, which failed to estimate the influence of varied drug combinations, although other opioids than remifentanil are much less-used.

Third, even if the included trials showed acceptable risks of bias, their heterogeneous clinical settings (e.g., difference in surgery type, assessed time points, and pain measurements (type of analgesics and scales) still influence results interpretation. The definitions of low- and high-dose for IAD were not standardized and even overlapped. This high heterogeneity limited a meta-analysis for data synthesis, decreasing the confidence of findings.

Fourth, this review may be in a risk of missing relevant studies due to the literature search was conducted by one person.

Implications for further study

Controlling IAD may benefit perioperative pain conditions. According to our findings, this control may represent administrating minimum-required intraoperative analgesics during insufficient anti-nociception. For achieving this, precise monitoring of intraoperative NAN balance is required. However, the results showed that there is no monitoring method presenting satisfying reliability. In considering the significance and deficiency in this field, we should make attempts to seek more reliable intraoperative nociception monitoring methods.

Human bio-fluids, such as saliva and blood, contain a variety of pain-related biomolecules (Jasim et al., 2018). Intraoperative nociception can activate endocrine glands and rise the secretion of stress hormones, such as cortisol (Desborough et al., 2000). Therefore, assessing endocrine response through monitoring biomolecules from human bio-fluids may indicate pain. Monitoring human bio-fluids, especially saliva, is achievable to operate during the surgery since it is less invasive, and allows a continuous monitoring. Due to opioids are able to suppress hormone secretions

(Seeber et al., 2019), the monitored hormone level and administered analgesics volume may potentially interact in a closed-loop fashion for guiding analgesia. This potential is uncertain but warranted for further investigations. This review did not find any methods developed based on monitoring human bio-fluids, thus, further relevant explorations are required.

CONCLUSION

This study investigated the methods to detect intraoperative nociception during the surgery. Two systematic reviews were conducted to explore the available methods and the significance on intra-and post-operative pain by guiding optimum intraoperative analgesic administration. In conclusion, maintaining intraoperative analgesics dosage at a sufficient but relatively low level may benefit postoperative pain conditions, however, no available method showed 99% sensitivity and specificity to detect intraoperative nociception precisely for guiding this preferred closed-loop analgesic administration. This study indicates the significance of exploring a reliable NAN monitoring method. Based on the possibilities of human bio-fluids for detecting pain, further investigations on bio-fluids for intraoperative nociception monitoring are recommended.

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