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Progress in Intraoperative Pain and Stress Monitoring: Current Technologies and Clinical Applications

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ABSTRACT

Perioperative analgesia and stress modulation are core components of precision anesthesia management. At present, there remains no unified, specific, and continuous objective monitoring standard for intraoperative nociception assessment. By retrieving relevant domestic and international research literature from 2019 to 2025, this paper systematically summarizes the pathophysiological basis, technical features, clinical evidence, and application key points of three categories of monitoring techniques: autonomic nerve-derived indicators (analgesia nociception index, surgical pleth index, nociception level index), pupillometry, and electroencephalogram-derived analgesia indices (qNOX, IoC2). Existing evidence shows that these techniques can reflect the intraoperative analgesia-nociception balance from different dimensions and assist in optimizing opioid titration, with application value in elderly patients, high-stimulation surgeries, and multimodal analgesia management. Future research should further clarify the applicable boundaries of different techniques, conduct high-quality multicenter studies to verify their value in improving patients' perioperative prognosis, and promote the clinical translation of multimodal monitoring and closed-loop analgesia systems.

Keywords: Intraoperative Pain; Stress Response; Nociception; Analgesia Monitoring; IoC2; Precision Anesthesia

Abbreviations: ERAS: Enhanced Recovery After Surgery; HPA: Hypothalamic–Pituitary–Adrenal; EEG: Electroencephalography; SPI: Surgical Pleth Index; ANI: The Analgesia Nociception Index; QoR: Quality of Recovery

Introduction

Clinical Significance of Intraoperative Pain and Stress Monitoring Anesthesia management consists of four fundamental components: hypnosis, analgesia, neuromuscular blockade, and stress response modulation. Quantitative monitoring techniques for depth of anesthesia and neuromuscular blockade have been well established in clinical practice, whereas intraoperative analgesia and stress response assessment still largely rely on indirect parameters, including blood pressure, heart rate, body movement, and sweating. With the increasing emphasis on precision anesthesia and enhanced recovery after surgery (ERAS), minimizing unnecessary opioid exposure while ensuring adequate analgesia has become an important clinical goal. Therefore, the development of objective monitoring approaches capable of continuously assessing the balance between analgesic efficacy and nociceptive stimulation is of considerable clinical importance. During general anesthesia, patients are unable to provide subjective pain reports; therefore, the primary target of intraoperative monitoring is nociception rather than pain perception.

Surgical stimuli, including incision, tissue traction, pneumoperitoneum, visceral manipulation, and tracheal intubation, activate peripheral nociceptors and transmit signals to the central nervous system. These stimuli subsequently trigger sympathetic activation, the hypothalamic-pituitary-adrenal (HPA) axis, and immune-inflammatory pathways, resulting in alterations in heart rate and blood pressure, increased release of catecholamines and cortisol, and activation of inflammatory and metabolic responses [1-3]. Insufficient analgesia may contribute to hemodynamic instability, excessive perioperative stress responses, and impaired [4]. postoperative recovery, whereas excessive analgesic administration may increase the risk of respiratory depression, postoperative nausea and vomiting, and delayed emergence from anesthesia. Therefore, the primary objective of intraoperative analgesic management is to maintain a dynamic equilibrium among surgical stimulation intensity, anesthetic depth, and individual patient characteristics.

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Concepts of Pain, Nociception, and Stress Response

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, whereas nociception refers to the neural encoding, transmission, and processing of noxious stimuli. Although closely related, these two concepts are not interchangeable [4]. In patients under general anesthesia, conscious perception and motor responses are largely suppressed; therefore, intraoperative monitoring is primarily aimed at assessing the balance between nociceptive stimulation and analgesic efficacy rather than directly quantifying pain intensity. The stress response represents a complex systemic reaction involving the nervous, endocrine, immune, and metabolic systems. In addition to nociceptive stimuli, perioperative stress responses can be influenced by various factors, including hypovolemia, hypoxemia, hypothermia, inflammation, and pre-existing diseases.

Therefore, objective intraoperative monitoring should be considered a complementary tool to support clinical decision-making, helping to identify inadequate analgesic protection or excessive drug effects. It should not replace comprehensive assessment integrating vital signs, surgical stimulation, anesthetic depth, and individual patient characteristics. Based on the source of physiological signals, current objective nociception monitoring technologies can be categorized into three levels: peripheral autonomic nervous system responses, brainstem reflexes, and cortical activity. These levels reflect distinct physiological processes and are influenced by different confounding factors, which may explain the discrepancies observed among monitoring indices in response to the same nociceptive stimulus (Table 1).

Table 1: Conceptual Differences among Pain, Nociception, and Stress Response.

Concept	Core Definition	Observable Intraoperative Manifestations	Key Considerations
Pain	A subjective sensory and emotional experience associated with actual or potential tissue damage	Assessed using VAS/NRS in awake patients	Cannot be directly assessed during general anesthesia
Nociception	Neural encoding, transmission, and processing of noxious stimuli	Autonomic responses, electroencephalographic changes, and pupillary reflexes	More suitable as an intraoperative monitoring target
Stress Response	Integrated neuroendocrine, immune, and metabolic responses	Fluctuations in blood pressure/heart rate and increases in hormonal and inflammatory markers	Affected by multiple factors, including volume status, medications, and underlying diseases

Peripheral Autonomic Nervous System

Peripheral autonomic nervous system-derived technologies indirectly reflect sympathetic–parasympathetic balance through physiological signals such as heart rate variability, pulse wave amplitude, skin conductance, and peripheral temperature. These approaches have the advantages of being non-invasive, continuous, and readily integrated with standard intraoperative monitoring systems. However, their interpretation may be affected by multiple confounding factors, including volume status, vasoactive medications, arrhythmias, body temperature, and autonomic nervous system dysfunction.

Brainstem Reflexes

The pupillary dilation reflex is integrated within the brainstem, and nociceptive stimulation can induce pupillary dilation through activation of this pathway. Compared with indices primarily dependent on pulse waveform or heart rate changes, pupillometry is relatively less influenced by peripheral circulatory conditions. Nevertheless, its accuracy may be affected by anticholinergic medications, opioids, ocular disorders, ambient light conditions, and measurement techniques. In addition, most currently available devices provide intermittent rather than continuous measurements.

Cerebral Cortex

Electroencephalography (EEG)-derived indices evaluate the interaction between nociceptive processing and analgesic effects by analyzing EEG characteristics associated with central nervous system activity. Their potential advantage lies in reducing dependence on peripheral autonomic responses. However, EEG-based measurements remain susceptible to interference from electromyographic activity, anesthetic agents, and baseline central nervous system conditions. The optimal target ranges for different patient populations require further validation. The above three categories of monitoring technologies reflect different physiological levels and each has specific advantages and limitations. In clinical practice, their application should rely on integrated interpretation of temporal trends and multimodal physiological information rather than isolated index values.

Conventional Monitoring Methods and Comprehensive Evaluation

Blood pressure, heart rate, body movement, sweating, lacrimation, and pupillary changes remain the most commonly used clinical indicators for assessing intraoperative analgesic adequacy. Although these parameters are easily obtainable, their specificity for nociceptive stimulation is limited. Hemodynamic responses can be influenced by various factors, including hypovolemia, pneumoperitoneum, anesthetic concentration, β-adrenergic blockers, vasoactive medications, and arrhythmias. Although biomarkers such as cortisol, catecholamines, blood glucose, lactate, and inflammatory mediators may reflect systemic stress responses, they cannot provide real-time feedback during surgery [5]. Therefore, conventional parameters remain fundamental components of perioperative safety monitoring, while objective nociception monitoring should be considered an adjunctive tool rather than a replacement for clinical assessment. This is particularly important in elderly patients, individuals with autonomic dysfunction, or patients receiving vasoactive drugs, in whom discrepancies between individual monitoring indices and clinical conditions may occur. In such situations, comprehensive interpretation based on multiple physiological parameters is essential.

Autonomic Nervous System-Related Monitoring Technologies

Autonomic nervous system-derived indices represent one of the most extensively investigated categories of objective nociception monitoring. Their common physiological basis is that noxious stimulation enhances sympathetic activity and suppresses parasympathetic activity, whereas opioids and regional anesthesia can attenuate these responses. The Surgical Pleth Index (SPI) is calculated from pulse wave amplitude and heartbeat interval derived from photoplethysmography signals, with values ranging from 0 to 100. In adults undergoing general anesthesia, an SPI value of 20–50 is commonly considered a reference range indicating an appropriate analgesia–nociception balance. Persistent SPI values >50 may serve as a warning threshold suggesting enhanced nociceptive responses. [6-8]. SPI enables continuous monitoring; however, interpretation should consider peripheral perfusion, body temperature, vasoactive medications, and cardiac rhythm changes. Additional analgesics should not be administered solely based on a single SPI measurement.

The Analgesia Nociception Index (ANI) is derived from the parasympathetic component of heart rate variability and ranges from 0 to 100. Intraoperative ANI values of 50-70 are commonly considered an appropriate reference range, whereas persistent values <50 may indicate insufficient analgesic protection [9,10]. ANI may assist opioid titration, including remifentanil administration; however, ANI values are affected by cardiac rhythm regularity, ventilation mode, age, anticholinergic medications, and β-blockers. Therefore, ANI values >70 should not be interpreted as definitive evidence of excessive analgesia. The Nociception Level Index (NOL) integrates multiple physiological parameters, including heart rate, heart rate variability, pulse wave amplitude, skin conductance, and peripheral temperature. Randomized controlled trials have demonstrated that NOL-guided analgesia may optimize fentanyl or remifentanil administration and potentially improve early postoperative pain management [11-14]. A target range of 10-25 is commonly reported. Persistent NOL values >25 may indicate increased opioid requirements, whereas values <10 may suggest the possibility of opioid reduction. Nevertheless, these thresholds should be dynamically interpreted according to device algorithms, anesthetic protocols, and surgical stimulation intensity.

Pupillometry

Pupillometry evaluates nociception through the pupillary dilation reflex or the Pupillary Pain Index (PPI). Randomized studies have suggested that pupillometry-guided administration of remifentanil or sufentanil may reduce intraoperative opioid exposure [15-17]. The PPI typically ranges from 1 to 9, with higher values indicating stronger nociceptive responses. Some cardiac surgery studies have used PPI ≥7 as a criterion for increasing sufentanil administration and PPI ≤3 as a criterion for opioid reduction [16,17]. However, because thresholds vary among devices, surgical procedures, and anesthetic regimens, PPI should be considered a stratification reference rather than a fixed dosing algorithm. The pupillary reflex is relatively less affected by peripheral circulatory conditions and may provide additional information in patients with hypotension or impaired peripheral perfusion. Nevertheless, ocular diseases, anticholinergic medications, opioids, ambient light, eyelid obstruction, and measurement procedures may influence results. Furthermore, the intermittent measurement mode of current pupillometry devices limits their application for continuous intraoperative monitoring.

EEG-Derived Indices and IoC_2 Monitoring

Electroencephalography (EEG)-derived monitoring technologies attempt to identify nociceptive responses from the perspective of central nervous system activity. The quantitative Consciousness Index (qCON) and quantitative Nociception Index (qNOX) are used to evaluate hypnotic depth and the probability of response to nociceptive stimulation, respectively. Within the Index of Consciousness (IoC) system, IoC_1 primarily reflects sedation depth, whereas IoC_2 is designed to assess analgesic status and nociception-related responses [18]. The qNOX is an EEG-derived index ranging from 0 to 99. Validation studies have commonly used values of 40–60 as a reference range, whereas values >60 suggest an increased probability of responding to nociceptive stimulation. However, its ability to discriminate different stimulation intensities and analgesic levels remains limited [19]. A randomized trial also used a qNOX target range of 30–50 for remifentanil titration, suggesting that intervention thresholds remain inconsistent [20]. IoC_2 also ranges from 0 to 99. A randomized study in breast surgery used 30-50 as the target range [21]. whereas a laparoscopic colorectal cancer surgery study suggested that 35-45 may be more appropriate in that specific clinical setting [22]. IoC monitoring has also been evaluated in elderly patients undergoing urological surgery, during stress responses induced by tracheal intubation, and in elderly patients undergoing laparoscopic colorectal surgery [23-25]. Currently, 30–50 may be considered a general reference range for IoC_2; however, it should not be regarded as a universal mandatory threshold across different devices and patient populations.

Comprehensive Evaluation of Clinical Evidence and Current Applications in China

Systematic reviews have demonstrated that, compared with conventional empirical analgesic management, objective nociception monitoring may reduce intraoperative opioid consumption, facilitate emergence from anesthesia, or decrease certain adverse events in selected studies. However, substantial heterogeneity exists among studies regarding surgical procedures, anesthetic protocols, and intervention thresholds [26]. A further validation review indicated that different monitoring devices emphasize different aspects, including nociceptive stimulus detection, drug-response assessment, or trend monitoring. Therefore, their clinical value depends largely on clearly defined monitoring objectives and appropriate clinical scenarios [27]. A network meta-analysis published in 2025 compared several nociception monitoring technologies, including ANI, SPI, NOL, and pupillometry. The results suggested that the effects of different monitors on opioid consumption and postoperative outcomes were not consistent, although pupillometry demonstrated potential advantages in reducing intraoperative opioid use [28]. Overall, current evidence has primarily focused on surrogate outcomes, such as opioid consumption and immediate hemodynamic changes, whereas evidence regarding patient-centered outcomes, including postoperative pain, delirium, gastrointestinal function, and recovery quality, remains insufficient. Research on nociception monitoring has also gradually expanded in China. Several single-center studies have investigated the application of IoC_1/IoC_2 monitoring in laparoscopic cholecystectomy, cesarean delivery under general anesthesia, and anterior cervical decompression and fusion surgery. These studies suggested that IoC monitoring may influence opioid or intravenous anesthetic titration, hemodynamic fluctuations, and certain early recovery outcomes; however, the direction and magnitude of medication changes were not consistent among studies [29-33]. Therefore, current evidence from China mainly supports the use of nociception monitoring as an adjunctive tool in addition to conventional monitoring rather than providing sufficient evidence for routine implementation or universal clinical benefit. Future studies should include larger sample sizes and focus on validating population-specific thresholds for ANI, SPI, NOL, pupillometry, and EEG-derived nociception indices.

Clinical Application Framework

Clinical application of nociception monitoring should follow the principles of trend-based interpretation, integrated assessment, and individualized management. During anesthesia induction and tracheal intubation, rapid changes relative to baseline values may provide important information regarding nociceptive responses. During the maintenance phase of anesthesia, monitoring trends should be interpreted in conjunction with specific surgical stimulation events, including skin incision, pneumoperitoneum, visceral traction, and bone manipulation. When ANI remains persistently <50, SPI remains >50, or NOL remains >25, and these changes are consistent with surgical stimulation and hemodynamic responses, analgesic administration may be adjusted stepwise according to evidence-based protocols [6-14]. If monitoring indices are inconsistent with blood pressure or heart rate changes, potential confounding factors such as hypovolemia, bleeding, medication effects, and signal quality should be evaluated before modifying analgesic therapy.

In elderly patients, individuals with autonomic dysfunction, patients with arrhythmias, or those receiving β-blockers and vasoactive medications, autonomic-derived indices should be interpreted with greater caution. Additional information from pupillometry or EEG-derived indices may improve clinical decision-making. During combined regional and general anesthesia, decreased nociception indices may reflect effective regional blockade rather than excessive analgesia and should not be interpreted in isolation. During emergence from anesthesia, residual opioid effects, sedation depth, spontaneous ventilation, and airway stimulation should be simultaneously evaluated to avoid medication administration based solely on predefined thresholds (Table 2).

Table 2: Clinical Interpretation and Management Strategies Based on Objective Monitoring Results.

Monitoring Findings	Potential Causes to Exclude First	Potential Management and Evidence Sources
Elevated index accompanied by increased blood pressure/heart rate	Intense surgical stimulation, inadequate analgesia, insufficient anesthetic depth	Adjust analgesia according to specific monitor thresholds; consider increasing hypnotic depth or reducing stimulation when necessary (RCTs/systematic reviews [8-19,28-30])
Elevated index accompanied by hypotension	Hypovolemia, bleeding, vasodilation, or measurement artifacts	Correct hemodynamic abnormalities first and reassess analgesic requirements thereafter (mechanistic studies/reviews [6-8,29])
Decreased index accompanied by hypotension/bradycardia	Excessive analgesia, excessive anesthetic depth, or vagal reflex	After excluding factors such as vagal reflex, consider reducing opioids or sedatives and managing circulation (titration trials/reviews [11-16,23,29])

Note: The proposed management strategies are derived from available randomized controlled trials, systematic reviews, and validation studies rather than formal GRADE recommendations. Clinical interventions should be individualized based on device-specific algorithms, patient conditions, and surgical stimuli.

Future Perspectives

Although intraoperative nociception monitoring has achieved preliminary clinical application, several challenges remain before these technologies can be transformed from research tools into standardized clinical pathways. Key issues include the optimization of thresholds, identification of appropriate patient populations, selection of clinically meaningful outcomes, and integration of multimodal technologies. First, multicenter and standardized studies are required to establish reference ranges and intervention thresholds across different age groups, surgical procedures, and anesthetic protocols. Particular attention should be given to generating population-specific evidence for high-risk groups, including elderly patients, individuals with autonomic dysfunction, and patients with cardiovascular diseases. Second, future research should extend beyond surrogate endpoints, such as opioid consumption and hemodynamic changes, toward patient-centered outcomes, including postoperative pain, delirium, postoperative nausea and vomiting, gastrointestinal recovery, Quality of Recovery (QoR) scores, and length of hospital stay. Furthermore, the cost-effectiveness and healthcare economic value of these monitoring strategies should be systematically evaluated.

Third, integration of peripheral autonomic signals, pupillary reflex responses, and EEG-derived parameters should be explored through multimodal monitoring approaches. Combined with baseline patient characteristics and surgical stimulation profiles, interpretable predictive models may provide a foundation for the development of closed-loop analgesia delivery systems. Fourth, standardized clinical guidelines and consensus frameworks are needed to define the appropriate patient populations, operational procedures, interpretation principles, and intervention strategies for different monitoring devices. This may help prevent inappropriate application of isolated thresholds across heterogeneous patient populations.

Conclusion

Intraoperative pain and stress monitoring are evolving from empirical hemodynamic assessment toward objective and multimodal evaluation strategies. Monitoring approaches including ANI, SPI, NOL, pupillometry, qNOX, and IoC_2 provide complementary information regarding the balance between analgesic efficacy and nociceptive stimulation through different physiological pathways, including autonomic nervous system activity, brainstem reflexes, and electroencephalographic responses. These technologies may facilitate individualized opioid titration and contribute to precision analgesic management.

However, current evidence remains limited by inconsistent thresholds, multiple confounding factors, and insufficient evaluation of patient-centered outcomes. In clinical practice, monitoring results should be interpreted based on temporal trends and integrated with surgical stimulation, vital signs, anesthetic depth, and patient characteristics rather than relying on individual index values alone. With further validation through multicenter studies, development of multimodal monitoring strategies, and establishment of standardized clinical pathways, objective nociception monitoring may play an increasingly important role in precision analgesia and perioperative stress management.

Conflict of Interest

All authors declare that they have no conflict of interest.

Author Contribution

Shichao Sun: Conceptualization, literature review, manuscript preparation, and initial drafting.

Ziheng Qi, Yuzhi Wei, and Wenyan Wu: Literature screening, data verification, and manuscript revision.

Siyi Yan: Academic supervision and manuscript revision.

Huan Zhang: Academic supervision and final manuscript review.

All authors have read and approved the final version of the manuscript.

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