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Evaluation of Pediatric Perioperative Pain through Analgesia Nociception Index (ANI): Systematic Review and Case Series

Elisa Verónica de Andrade Pires

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Evaluation of Pediatric Perioperative Pain through Analgesia Nociception Index (ANI): Systematic Review and Case Series

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Elisa Verónica de Andrade Pires

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Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto

Endereço de correio eletrónico: up201807676@up.pt

Orientadora

Dra. Sónia Macedo Martins Duarte

Assistente Hospitalar do Serviço de Anestesiologia – Unidade Local de Saúde de Santo António

Afiliação: Colaboradora Externa, Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

Endereço de correio eletrónico: soniamacedoduarte@gmail.com

Coorientador

Professor Doutor Humberto José da Silva Machado

Assistente Graduado Sénior do Serviço de Anestesiologia – Unidade Local de Saúde de Santo António

Afiliação: Professor Catedrático convidado, Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

Endereço de correio eletrónico: hjs.machado@gmail.com

Abril de 2024

Assinatura da Estudante

Verónica Pires

Assinatura da Orientadora

[illegible]

Assinatura do Coorientador

Humberto Machado

Porto, abril de 2024

Dedication

À minha família, pelo apoio e incentivo incondicionais.

Aos meus amigos, pela amizade, alegria e motivação. Tornaram este percurso mais feliz.

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Resumo

Introdução:
O *Analgesia Nociception Index* (ANI) é um monitor de nociceção que se baseia na interpretação da variabilidade da frequência cardíaca enquanto reflexo do tónus parassimpático. Ao fornecer continuamente uma medida da nociceção, visa personalizar a analgesia intra e pós-operatória.
Apesar dos avanços na monitorização da nociceção na população adulta, nos doentes pediátricos os dados existentes são limitados. Assim, esta dissertação tem como objetivo rever a utilização deste monitor na população pediátrica, no bloco operatório e na Unidade de Cuidados Pós-Anestésicos, de modo a avaliar a sua eficácia e aplicabilidade, bem como comparar o ANI com outros métodos de monitorização de analgesia e nociceção.

Metodologia: A Revisão Sistemática foi realizada segundo as *guidelines* PRISMA, de acordo com o método PICO (*Population, Intervention, Comparison, Outcome*). Foram pesquisados estudos em língua inglesa, com data igual ou posterior a 2018, nas bases de dados PubMED e Cochrane Library, utilizando as palavras-chave "(pediatric OR children) AND (analgesia nociception index)". Os artigos incluídos exploram a utilização do ANI como método de monitorização de nociceção e de analgesia na população pediátrica no perioperatório. Foram excluídos os artigos relativos a doentes em cuidados intensivos, à população adulta e artigos duplicados.
Adicionalmente, após aprovação da Comissão de Ética (N/REF.a 2023.240(CC-DEFI/192-CE) e obtenção do consentimento informado dos representantes legais, foram recolhidos casos clínicos ilustrativos da aplicação do ANI em pediatria.

Resultados/Discussão: Foram incluídos 6 artigos originais e 4 artigos de revisão. Da sua análise, é possível inferir que, na população pediátrica, o ANI é capaz de identificar estímulos nocicetivos, revelando-se mais preciso do que os parâmetros hemodinâmicos, e de detetar o restabelecimento de analgesia adequada. Na Unidade de Cuidados Pós-Anestésicos, demonstrou também resultados promissores, evidenciando uma correlação com as escalas de auto e heteroavaliação da dor. Nesta dissertação, são ainda apresentados 5 casos clínicos, que permitiram demonstrar a existência de uma correlação negativa entre o ANI e a frequência cardíaca, tendo-se também constatado, quase invariavelmente, que a administração de fentanil, quando os valores de ANI sugeriam nociceção, resultou numa elevação dos mesmos para valores indicativos de analgesia suficiente nos 5 minutos seguintes.

Conclusão: O ANI tem mostrado ser uma ferramenta fidedigna de monitorização da nociceção na população pediátrica. A sua utilização nesta faixa etária deve, contudo, continuar a ser alvo de estudo, sendo pertinente avaliar o impacto da utilização do ANI na redução do consumo de opióides, bem como compará-lo com os outros métodos de monitorização de nociceção existentes.

Palavras-chave: Avaliação da dor; analgesia; nociceção; pediatria; anestesia pediátrica

Abstract

Introduction: The Analgesia Nociception Index (ANI) is a nociception monitor that relies on the interpretation of the heart rate variability as a reflection of the parasympathetic tone. By continuously providing a measure of nociception, it aims to personalize intra- and post-operative analgesia. Despite the progress in nociception monitoring in adult population, pediatric data are limited. Thus, this dissertation aims to review the use of ANI in children, both in the operating room and in the Post-Anesthesia Care Unit, to assess its effectiveness and applicability. Additionally, it seeks to compare ANI with other methods of analgesia and nociception monitoring in the pediatric context.

Methods: The systematic review was conducted following PRISMA guidelines, according to PICO (Population, Intervention, Comparison, Outcome) method. English-language studies published in 2018 or later, from PubMed and Cochrane Library databases were included, using the keywords "(pediatric OR children) AND (analgesia nociception index)". The included articles explore the use of ANI as a nociception monitor in pediatric patients during the perioperative period. Articles related to intensive care, adults, as well as duplicates were excluded.

Additionally, following approval from Ethics Committee (N/REF.a 2023.240(CC-DEFI/192-CE) and obtaining informed consent from patients' legal representatives, illustrative clinical cases applying ANI were collected.

Results/Discussion: Six original studies and four reviews were included. From that analysis, ANI seems able to identify nociceptive stimuli, being more accurate than the hemodynamic parameters, and to detect the re-establishment of adequate analgesia. In the Post-Anesthetic Care Unit, it also showed promising results, correlating with self and hetero-assessment pain scales. This dissertation also presents five clinical cases, which demonstrate the existence of a negative correlation between ANI and heart rate. It was also consistently observed that the administration of fentanyl, when ANI values suggested nociception, resulted in an increase in these values to levels indicative of adequate analgesia in the following five minutes.

Conclusion: ANI has proven to be a reliable tool for monitoring nociception in the pediatric population. Its use in this age group should, however, continue to be studied, and it is important to evaluate the impact of using this monitor on reducing opioid consumption, as well as to compare it with other existing nociception monitors.

Keywords: Pain measurement; analgesia; nociception; pediatrics; pediatric anesthesia

List of Abbreviations

ANI – Analgesia Nociception Index

ANI_i – Instantaneous Analgesia Nociception Index

ANI_m – Mean Analgesia Nociception Index

ANS – Autonomous Nervous System

ASA-PS – American Society of Anesthesiologists Physical Score

AUROC – Area under the receiver operating characteristic

BIS – Bispectral index

BP – Blood pressure

DBP – Diastolic Blood Pressure

FLACC – *Face, Legs, Activity, Cry and Consolability*

FLACC-R – *Face, Legs, Activity, Cry and Consolability - Revised*

HR – Heart rate

HRV – Heart Rate Variability

MBP – Mean Blood Pressure

NIPE – Newborn Infant Parasympathetic Evaluation

NOL – Nociception Level Index

PACU – Post-anesthetic care unit

PAED – Pediatric Anesthesia Emergence Delirium

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PICO – Population, Intervention, Comparison, Outcome

OR – Operating room

SBP – Systolic Blood Pressure

SCA – Skin Conductance Algesimeter

SPI - Surgical Plethysmographic Index

ULSSA – Unidade Local de Saúde de Santo António

Index

List of Tables

List of Figures

Introduction

The *International Association for the Study of Pain* (IASP) defines pain as an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage[1]. This relates to a subjective feeling, which is why it differs from the concept of nociception, which corresponds to the physiological process of the nociceptive stimulus[2]. Thus, under general anesthesia, cortical integration does not occur, so the subject does not experience pain. However, the surgical stimulus activates the neurological pathways involved in pain transmission, which culminates in the phenomenon of nociception[3].

Considered the 5th vital sign, pain embraces sensory, cognitive, behavioral, and cultural components. During the perioperative period, it is frequently experienced, and its adequate evaluation and management is a key element for the recovery process after a surgical procedure. Moreover, proper perioperative pain control has been associated with a reduction of postoperative complications, reduced length of hospital stay, and faster recovery[4].

To date, in clinical practice, there is still no universally accepted device to monitor, directly and non-invasively, the pathways involved in nociception. Therefore, given that pain is indissoluble from subjectivity and individual differences in perception, its assessment becomes complex.

When evaluating pain in pediatric patients, it can be challenging to assess its intensity and quality due to children's early stage of language development, which may limit their ability to express their discomfort. The diverse cognitive and affective traits further hinder accurate pain evaluation and treatment. Indeed, evidence suggests that pediatric acute, recurrent and chronic pain, are not ideally approached[5].

Over time, several tools have been developed to overcome these difficulties. To date, the three main methods for pain evaluation are self-assessment scales, hetero-rating scales, and the use of physiological indicators. Those tools can be used separately or in combination[5].

Self-assessment scales rely on the child's ability to quantify and describe their pain. It can require asking the child to indicate the facial expression that best represents their perception of pain, as with the Wong-Baker faces scale (Figure 1), to assign a numeric value to their pain, using the Numerical Rating Scale, or to identify, in a 10cm line, a point that corresponds to the intensity of the pain, as in the Visual Analogue Scale.

Self-assessment scales can be applied in a verbal or non-verbal format, although demanding an adequate level of cognition, and they must be preferred, whenever possible, in children over 3 years old, without cognitive deficits, and who are not in a state of excessive suffering. Considering those criteria, the Numerical Rating Scale is reserved for older children, generally older than 8 years old[5,6]. Pain intensity, anxiety and emotional reaction can limit the accuracy and applicability of those scales.[7]

Hetero-rating scales correspond to an indirect measurement of pain and rely on physical indicators, representing the reactivity to pain. Those scales consider the interpretation of factors such as facial expression, movements, crying, or a combination of them, such as Neonatal Infant Pain Scale (NIPS) (Table I), Face, Legs, Activity, Cry, Consolability (FLACC) (Table II) and Face, Legs, Activity, Cry, Consolability – Revised (FLACC-R) (Table III)[5,6]. Hetero-rating scales have several limitations because they rely on subjective evaluation and cannot be used in patients under general anesthesia.

While for the evaluation of one of the anesthesia cornerstones, the hypnosis, adequate monitoring tools have already been developed and validated, based on the processed electroencephalogram (as Bispectral Index (BIS™)), the analysis of the other central anesthesia element, analgesia, is still mainly empirical. Therefore, during general anesthesia, nociception and analgesia are typically assessed by interpreting changes in heart rate (HR), blood pressure (BP), and clinical signs like movement or sweating. Nevertheless, guidance based on hemodynamic parameters is associated with low sensitivity and specificity, since other factors, such as hypovolemia, reversal of neuromuscular blockers, beta-blockers use, as well as an inadequate anesthetic depth may act as confounding factors[9–11]. This can lead to unnecessary or inadequate analgesic administration, commonly opioids. The use of insufficient opioid doses can lead to nociceptive stress, hypertension, tachycardia and cardiac events, and, in the long term, can be associated with a higher incidence of chronic pain and hyperalgesia[11,12]. In contrast, excessive opioid doses have been associated with hypotension, bradycardia, respiratory depression, slower awakening after anesthesia, postoperative *delirium* and desensitization of μ receptors, reducing opioid efficacy on postoperative analgesia [9,13,14]. Thus, the use of tools for a more accurate titration of opioids can yield significant benefits.

It is known that nociceptive stimuli trigger autonomous nervous system (ANS) responses, with an increase in sympathetic activity and a decrease in parasympathetic activity[2]. During the last decades, several studies have shown that those stimuli resulted in changes in cardiac activity, blood vessels, pupils and sweat glands, and, therefore, techniques to infer nociception through the monitoring of those peripheral effectors were developed.[2,3,11]

Examples of tools studied to monitor nociception in the pediatric population are the pupillometry (that considers the measurement of the pupil diameter to assess ANS activity, considering that there is a reflex pupil dilation in response to nociception), the Skin Conductance Algesimeter (SCA) (that evaluates the activity of the electric conduction on the skin surface as a measure of the sweat efflux triggered by the increased sympathetic activity), the Surgical Plethysmographic Index (SPI) (that corresponds to the analysis of the waveform and heartbeat of photoplethysmography in pulse oximeters), the Analgesia Nociception Index (ANI) (based on the heart rate variability (HRV)), the Newborn-Infant Parasympathetic Evaluation (NIPE) (a version of ANI designed to be used in neonates and infants, as they present a lower HRV, due to their immature ANS and higher HR) and the Nociception Level Index (NOL) (a multiparametric monitor which integrates the amplitude of the photoplethysmographic pulse wave, temperature, skin conductance, HR, HRV and their time derivatives)[3,11,15]. Pupillometry, NOL, SPI and SCA indexes increase with nociception, while ANI and NIPE present an inverse relationship with it. Currently, none of these techniques has been established or is consensually used. The ideal nociception monitor should customize analgesia and opioid doses precisely, and detect nociception faster than hemodynamic changes, thus preventing postoperative pain[3].

ANI™, developed by MDoloris, is a non-invasive method of parasympathetic tone assessment, based on the analysis of HRV[11,16].

Parasympathetic activity determines respiratory variability of heart rate, to the extent that, if low, i.e. in the presence of a nociceptive stimulus, the interval between heartbeats exhibits a decreased variability, while if high, respiratory variability will be more significant[17]. So, the ANI principle is based on the reduction of the parasympathetic tone, triggered by nociceptive stimulus, and each breath cycle provides immediate information about the parasympathetic activity, allowing, through the analysis of R-R intervals on the EKG, the development of a graph that demonstrates the HR variations associated with breathing.

Considering it only depends on two thoracic electrodes and does not require any invasive procedure, it is a tool that promotes patient comfort and safety while being very simple to use[18].

The ANI monitor (Figure 2) displays two values: ANI_i, the instantaneous value, that represents the mean value from the last 120 seconds, and ANI_m, based on the mean value from the last 240 seconds[9]. Those are expressed on a 0 to 100 scale, 100 corresponding to maximum parasympathetic tone, comfort and analgesia, and 0 reflecting minimum parasympathetic tone, with maximum nociception and stress[9]. In patients under anesthesia, the ideal values should range between 50 and 70[19]. It can also be interpreted as a tool for predicting hemodynamic changes. In other words, if there is a reduction in ANI, there is a higher likelihood of experiencing hemodynamic changes such as an increase in BP or HR, by around 20%, within the next 10 minutes[20].

This monitor was designed to be used in the operating room (OR), in patients under general anesthesia, however, it is also being used in conscious patients, namely in the Post-Anesthesia Care Units (PACU).

Although it was designed to be used in people over 2 years old, most of the studies that assessed the usefulness of ANI as a method of intra and postoperative nociception monitoring have focused solely on adult patients, in whom its use is recognized as a promising tool of accurate nociception monitoring. In adults, the use of ANI demonstrated an 88% sensitivity and 83% specificity to predict hemodynamic changes after a nociceptive stimulus, and it was associated with a reduction in intraoperative opioid use[11,21]. Nonetheless, in pediatric anesthesia, data availability is more limited.

Therefore, it is pertinent to assess the applicability of ANI to monitor intra- and postoperative analgesia in pediatric patients.

Methods

This systematic review was conducted according to *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines, following the PICO *(Population, Intervention, Comparison, Outcome)* method:

- *Population:* Children during the perioperative period;
- *Intervention*: Use of ANI as a tool for nociception and analgesia monitoring;
- *Comparison*: Other methods for evaluation of pain and nociception in children, namely hemodynamic data, self- and hetero-assessment scales for pain evaluation, as well as other nociception indexes (pupillometry, SCA, SPI, NOL, NIPE);
- *Outcome*: Evaluate the usefulness of ANI in monitoring nociception and optimizing analgesia for perioperative pediatric patients.

PubMed and Cochrane Library databases were used, with the following research terms: "(pediatric OR children) AND (analgesia nociception index)", to select articles that explored the use of ANI in the pediatric population. A publication date from January 2018 to January 2024 was considered, with articles published in English language.

Exclusion criteria included duplicates, studies about pediatric intensive care patients and studies focused on the adult population. In addition, articles that only addressed other nociception indices, without adding information about ANI, were excluded. Inclusion and exclusion criteria are exhibited in Table IV.

In the first selection phase, the titles and abstracts of the studies were analyzed and, according to their relevance and inclusion criteria, they were divided into three categories: "to include", "to exclude" or "in doubt". After this first analysis, the full text from articles marked as "to include" and "in doubt" was read, obtaining the final group of selected studies.

Additionally, illustrative case reports of ANI clinical application in children during the perioperative period were collected at Unidade Local de Saúde de Santo António (ULSSA), during February 2024. This recruitment of patients was approved by the Hospital Ethics Committee (N/REF.a 2023.240(CC-DEFI/192-CE)) and informed consent from children's legal representatives was obtained.

Results

Following the strategy above mentioned, 36 studies were found in PubMed and 15 in Cochrane Library. After selection, 10 studies were included, 6 original studies and 4 narrative reviews, used as secondary sources. The process of study selection is represented in Figure 3. The general characteristics of the original studies are presented in Table V. Table VI presents the main conclusions from the reviews analyzed.

The studies were divided into three groups, according to their goals: assessment of ANI as an intraoperative nociception monitor, the use of ANI for postoperative pain monitoring and comparison of ANI with other nociception monitoring tools.

1. <u>ANI as a tool for monitoring intraoperative nociception</u>

Julien-Marsollier et al. aimed to evaluate the capacity of ANI to detect nociception in children, collecting, 5 minutes before and after the surgical incision, ANI_i and ANI_m, and calculating DeltaANI (DeltaANI = (ANI_i – ANI_m)/ANI_m). During surgery, analgesia with remifentanil was adjusted according to hemodynamic changes. 83.3% of patients presented a reduction of all ANI parameters after a nociceptive stimulus, the remaining 16.7% were considered non-responders. ANI_i reached the nadir (58), 80 seconds after the surgical incision, and ANI_m reached the nadir (60), 200 seconds after the incision. Maximum values of HR and MBP were reached after 200 and 300 seconds, respectively. The area under the receiver operating characteristic (AUROC) was >0.75 for all ANI parameters, while for SBP, DBP and MBP there was a value only slightly, but significantly different, from the random classifier[12].

In another study conducted by *Weber et al.*, in pediatric surgical patients with supplemental caudal block, there was a reduction in ANI_m 2 minutes after the surgical incision, from 82±19 to 68±21 (p = 0.019) – still within the limits of adequate antinociception –, with no changes in ANI_i or HR. In addition to its usefulness in providing information about nociception, this group also compared the predictive value of ANI and HR to guide the decision to increase opioid doses. The pediatric anesthesiologist was blinded to ANI values, so the decision to administer opioids was independent of that parameter, and increased HR was the most frequently reported reason for opioid administration. In patients with ANI_i<50 at the time of the decision to give additional opioids, the value started to increase 60 seconds after fentanyl administration and, 120 seconds later, ANI_i returned to the value prior to the decision to increase analgesia, while ANI_m and HR values remained unchanged. On the other hand, patients with ANI_i≥50 at the moment of decision – suggestive of adequate analgesia –, showed no change in ANI_i, ANI_m or HR after opioid administration. In situations where opioid administration was due to patient movements, all three parameters remained unchanged[9].

Sharma et al. aimed to compare changes in ANI values with variations in hemodynamic parameters and with SPI, before and after opioid administration. In this study, the anesthesiologist's criteria for administering fentanyl boluses were the clinical data (HR and MBP) and/or SPI and were not guided by ANI. HR, MBP, SBP, DBP, SPI, ANI_i and ANI_m were recorded at baseline – before drug administration – and during various nociceptive stimuli. The correlation between ANI_i and ANI_m values with the hemodynamic parameters and SPI was moderately strong and negative ($P < 0.001$) for all variables, being stronger for ANI_i than ANI_m. Thus, increases in HR, MBP and SPI correlated with a decrease in ANI_i and ANI_m values. It was also noted that in patients with $ANI_i<50$, it increased to beyond 50 after fentanyl administration, which was statistically significant ($p<0.05$) at 3, 4, 5 and 10 minutes[10].

2. <u>Postoperative pain</u>

Tiryaki et al. evaluated the existence of a correlation between the traditionally used pain scales – FLACC, Wong-Baker Faces and Numerical Rating Scale – and the values displayed on the ANI monitor. This study included adolescents (12-17 years old) who had undergone laparoscopic appendectomy. To reduce subjectivity, all measurements were recorded by the same evaluator. A statistically significant difference was found between the measurements of the different scales ($p<0.05$) and there was no statistically significant difference between ANI_i and ANI_m ($p> 0.05$). A statistically significant negative correlation was also identified between pain scales and ANI measurements, meaning that an increase in the values of the pain scales was associated with a reduction in ANI values[19].

Another study, by Sharma *et al.*, looked for the existence of a correlation between ANI and FLACC-R scale for the prediction of acute postoperative pain at PACU, in children between 2 and 12 years old. A statistically significant strong negative correlation was identified between ANI_i and ANI_m and FLACC-R ($r= -0.89$, $P < 0.001$ and $r= -0.88$, $P < 0.001$, respectively), during stay at PACU[10]. The correlation between BP and FLACC-R, despite also being statistically significant, was only moderate ($r = 0.74$, $P < 0.001$)[10].

Evrard *et al.* assessed whether ANI could predict the need for morphine at PACU, in children aged between 2 and 7 years old, undergoing tonsillectomy. After the procedure, general anesthesia was maintained for 4 minutes, to obtain ANI_m. In the PACU, children were evaluated by an independent nurse every 10 minutes, using FLACC scale, and a dose of 0.1mg/kg of morphine was administered if they scored higher than 3. It was found that the ANI_m value measured at the end of the surgery was not able to predict postoperative morphine consumption (ANI_m AUROC=0.54, 95%

CI [0.42-0.65], and p=0.57). Additionally, there was no correlation between ANI_m and maximum FLACC scale score at PACU[22].

3. <u>Other nociception monitors</u>

3.1. Surgical Pleth Index

As previously mentioned, *Sharma et al*. designed a study that compared the changes in ANI values and SPI during pediatric neurosurgery, before and up to 10 minutes after opioid administration. The main effect of time showed a statistically significant and positive change in ANI_i after an opioid bolus, while the change in SPI was not statistically significant over time. Furthermore, the nociception group (baseline ANI_i<50) showed a higher change in ANI_i, compared to the antinociception group (baseline ANI_i>50) at that time point. This difference was not statistically significant for ANI_m and SPI at any time point following opioid administration[10].

3.2. NIPE

A study by *Lebrun et al.* reported evidence of a significant effect of the stimulation intensity on NIPE response. In children under sevoflurane anesthesia, they applied three tetanic stimulations, with different intensities, and assessed NIPE after each stimulus. The intensity of the stimulus influenced significantly the NIPE variation (p<0.001) but not HR (p=0.52)[23]. This is not in line with what was observed for ANI, where different intensities of tetanic stimuli did not have a statistically significant impact on ANI values in children under anesthesia[24].

3.3. Pupillometry

Evrard et al. evaluated pupillometry, along with ANI, and their prognostic value for detecting postoperative pain and morphine needs at PACU. Neither of the monitors were able to predict postoperative morphine use, and no correlation with maximum pain score, according to FLACC, was verified[22].

3.4. Nociception Level Index

Chemam et al. evaluated NOL to validate its capacity to quantitatively assess nociception in children under anesthesia with sevoflurane and alfentanil. Before surgical incision, three tetanic stimuli of different intensities (10-30-60 mA) were applied, in a random sequence, separated by 5-minute intervals (to allow the return to baseline), and NOL, HR, BP and ANI values were registered. NOL increased after each stimulus (p<0.05) and the increase was influenced by the intensity of the stimulus (p<0.001). In turn, HR and BP were not significantly changed by the stimuli. ANI decreased after each stimulus ($p<0.001$), however the response was not influenced by the intensity of the stimulus ($p=0.064$). There was also a significant correlation between NOL and ANI ($r=0.47$; $p<0.001$)[24].

Discussion

1. ANI as a tool for monitoring intraoperative nociception

The results assembled in this review allow us to conclude that the ANI monitor can successfully identify intraoperative nociception in pediatric patients[10,12]. Whether comparing ANI before and after surgical incision or evaluating the response to other nociceptive stimuli and combining it with hemodynamic data, it is possible to demonstrate that ANI has diagnostic value for the detection of nociception in children between 2 and 17 years old. However, it should be highlighted that ANI_i and DeltaANI exhibit better sensitivity, specificity and predictive value than ANI_m, which requires a longer interval to reflect the effect of nociceptive stimuli and has a higher percentage of dubious values[12]. The same conclusion was presented by *Weber et al.*, which showed that, unlike ANI_i, which increases after an opioid bolus (fentanyl 1mcg/kg), reflecting sufficient antinociception at 2 minutes, ANI_m was not able to identify antinociception, with no change after opioid bolus. *Sharma et al*. also demonstrated that ANI_m is a worse indicator than ANI_i, which can be attributed to the fact that 4 minutes might be too long to translate instant changes in the nociception/antinociception balance[9,10].

On top of that, ANI shows a higher predictive value in detecting nociceptive stimuli compared to hemodynamic data, which have a low or non-existent predictive value. In fact, in the selected studies, hemodynamic parameters either took longer than the ANI monitor to translate nociception or remained unchanged after the stimuli[9,12,24]. Therefore, it's possible to point out that ANI can alert to the need of analgesia adjustment before the development of a clinically evident nociception response.

However, it was also found that some children show no reduction in ANI values when submitted to painful stimuli. That can be explained by factors such as interpersonal variability in sensitivity to opioids or the effect of anesthetic agents on the modulation of the parasympathetic nervous system.

In addition, ANI also proved to be able to provide information on the re-establishment of sufficient analgesia after opioid administration and it seems to be superior to HR for the assessment of this phenomenon[9]. Therefore, it seems possible to use ANI as a guide for nociception/antinociception balance in pediatric population submitted to surgery.

A weakness stressed in some of the included studies is that the evaluation of ANI's ability to monitor nociception was based on its comparison with the hemodynamic data, although it is now generally accepted that these parameters are poor predictors of insufficient analgesia[3,9]. Additionally, considering that there is no external validation of ANI value, *Julien-Marsollier et al.*'s study, which compared ANI values before and after surgical incision, creates a bias factor, as the use of a pre-stimulus ANI as a standard reference could be considered inappropriate. Finally, the same study underlines that no drugs with influence on the ANS were used in their research, so extrapolation of conclusions to standard anesthesia should be cautious, as many drugs could exert effect over this system (namely alpha-2 adrenergic receptor agonists)[12,25].

To date, there is no data on the benefit of ANI use in the reduction of intraoperative opioid use in pediatric patients. This has already been assessed for other nociception monitors, such as pupillometry[3]. In adults, *Dundar et al.* guided intraoperative remifentanil infusion according to ANI, in patients submitted to breast surgery under general anesthesia and paravertebral block, and concluded that the ANI group presented a significantly lower intraoperative remifentanil dose than the control group, in which the infusion was guided by hemodynamic data[26]. Thus, future studies should be performed to assess ANI's ability to reduce intraoperative opioid consumption in the pediatric population.

2. <u>Postoperative pain</u>

Regarding ANI's usefulness in evaluating postoperative pain at PACU, when compared with self and hetero-assessment pain scales, such as FLACC, Wong-Baker Faces and Numerical Rating Scale, a correlation was described between those scales and ANI. Unlike the above-mentioned scales, ANI has the advantage of continuously displaying a pain intensity value[19].

Contrary to what was shown for intraoperative use of ANI, where it seems unable to differentiate pain quantitatively, in the postoperative period of neurosurgical pediatric patients, it has exhibited a strong negative correlation with FLACC-R scale, being able to distinguish between weak, moderate and strong pain, which is beneficial for analgesia titration[10].

It is important to note that anxiety and fear can affect children's facial expressions and behaviour, which can lead to an overestimation of their pain when assessed using hetero-assessment scales. Thus, ANI could be a way to circumvent these biases and provide a more accurate evaluation, and it seems able to allow a fast and effective response to the need of analgesia optimization[22].

However, in awake patients, some other confounders, absent in unconscious patients under anesthesia, should be considered when interpreting ANI. Namely agitation or discomfort, with effect on the sympathetic nervous system, can interfere with cut-off values interpretation to classify analgesia as adequate.[10]

Considering ANI_m's capacity to predict morphine need in the postoperative period, guided by FLACC scale, its use was not supported by the included studies, with no correlation found between ANI values, maximum pain scale and morphine consumption. *Evrard et al.* present as a possible explanation for this lack of correlation the fact that ANI was measured while the child remained under general anesthesia with sevoflurane, in identical concentration to the one maintained during surgery. The authors believe that the sevoflurane dose might have caused a decrease in sympathetic nervous system activity, which may have underestimated postoperative nociception[22]. Nevertheless, this possible effect was not observed in other studies that assessed ANI use in children under sevoflurane anesthesia[3,9,24].

Lim's review mentions studies carried out on adults that question the applicability of ANI in conscious patients, arguing that in awake adults, the correlation between HRV and pain intensity is controversial[15]. This is supported by a study by *Ledowski et al.,* which aimed to compare ANI values with Numerical Rating Scale in the assessment of post-operative pain, and showed that the sensitivity and specificity of ANI values were only 50% when distinguishing absence of pain from severe pain[27]. However, *Boselli and Jeanne* developed a similar study and concluded that there was a statistically significant negative correlation between ANI and Numerical Rating Scale[28]. *Boselli and Jeanne* raised the hypothesis that the disparity of results between the two studies might be related with the hypnotic drug used for maintenance of general anesthesia.

Despite confounding factors should be considered, some studies suggest potential interest in the use of ANI for postoperative pediatric pain management, so more studies, with larger samples, should be performed to clarify this hypothesis.

3. Other nociception monitors

SCA presents interesting results for nociception monitoring in awake neonates and infants. This monitor has the advantage of being independent of blood volume, cardiac activity and the use of vasoactive drugs, exhibiting a more specific correlation with pain and nociceptive stimuli[11,15]. However, under general anesthesia, there is insufficient data to conclude about its ability to evaluate pain quantitatively, as surgical levels of anesthesia might inhibit sympathetic tonus, masking skin conductance response[3]. Thus, future studies are needed to assess its efficacy in children under general anesthesia.

SPI revealed limited applicability in pediatrics, contrary to what was reported for adult patients.[15] This can be related to the differences in blood vessels distensibility, vascular tone and higher basal HR of pediatric patients[10].

For neonates and infants, NIPE seems to be more effective than any other index for nociception and analgesia monitoring, with proven usefulness in quantitative and qualitative nociception monitoring, unlike ANI, which, in anesthetized children, only demonstrated evidence for qualitative assessment. As NIPE is an ANI version specifically designed for younger children, this difference is somehow unexpected. However, it might be justified by the fact that the time between the nociceptive stimuli was different in the two studies that draw these conclusions. In the study that reported that the effect of the stimulation intensity on the amplitude of ANI variation was not significant, the interval between stimuli was set at 5 minutes (because the primary aim was to study NOL and they had concluded that NOL required 2-3 minutes to return to baseline). On the other hand, in the NIPE study, although the interval between stimuli was also 5 minutes, the time needed for the value to return to baseline was 6±1 minutes. So it was hypothesized that 5 minutes might be a too short interval to allow ANI values to return to baseline and that this fact might have compromised the results[24].

Pupillometry presents satisfying results and might be a promising tool for nociception monitoring in pediatric perioperative period, as its use to guide analgesia resulted in a significant reduction in opioid use. Actually, pupillary dilation reflex is stronger in children, which seems related to the impact of brain maturation in the sensitivity of the different brain structures involved in this reflex[3]. However, it presents three main disadvantages: the eyelid must be kept open during surgery for evaluation, it does not provide continuous monitoring, and some factors can influence pupillary diameter, as ambient light, severe anxiety and drug effects[7,15]. *Bertolizio et al.* reported in their review that there is only one study to date that compared pupillometry with ANI, having shown that pupillometry might present a slightly lower sensitivity but higher specificity[11].

NOL proved to be sensitive to nociceptive stimuli, and its variation was related to the intensity of the stimulus, in children between 5 and 12 years old, under sevoflurane anesthesia. Unlike ANI, in the studied population, NOL stood out for allowing a quantitative evaluation of nociception. By offering both qualitative and quantitative nociception monitoring, this tool shows potential for guiding intraoperative analgesia in children, but more evaluation is required[24].

Considering the pediatric physiological specificities, namely higher heart and respiratory rates, it is urgent to readjust the ideal range of adequate antinociception for each monitor to children, which may differ from the intervals set for adult patients. Theoretically, NOL values ranging from 10 to 25 are considered ideal for adequate analgesia, however, a study in pediatric patients showed that all patients presented a value below 10 before the nociceptive stimulus, and a maximum value of 24±9 after the most intense stimulus[24]. Likewise, SPI reference values for adults do not seem adequate for children, considering the differences in vascular tone, muscle and catecholamine concentrations, that affect pulse wave amplitude, a major component of SPI, thus interfering with the values considered ideal. In this regard, the optimal range for SPI in children should probably be lower[3,15].

Although none of the available monitors to date is considered ideal, since they all have some limitations, their results have proven to be more solid and reliable than the use of hemodynamic parameters alone. Therefore, the use of nociception indexes should be instituted and privileged over the traditional methods to complement nociception evaluation and management[11].

The available literature comparing the use of ANI in pediatrics with other nociception monitors is scarce, which prevents the drawing of conclusions about the most beneficial nociception monitor in the pediatric population. However, it should be noted that ANI, unlike other monitors, has proven to be useful not only in detecting intraoperative nociception, but also in monitoring postoperative pain in pediatric patients[15].

4. Implications for clinical practice

A pain monitoring tool like ANI has the potential to be useful for future indications. In the future, it may be feasible to develop protocols that have pre-defined opioid doses according to ANI values, to rapidly restore antinociception after a decline in the monitor value. Additionally, it could be particularly interesting in patients with chronic pain, who would benefit from continuous pain monitoring and management.

The reduced number of specific studies about ANI in pediatrics translates into a lack of evidence to clarify the interest of its use, since, due to their physiological, pharmacokinetic and pharmacodynamic differences, it is not possible to extrapolate results and conclusions of studies in adult population to children. It should, however, be noted that the high-frequency component of HRV, which expresses the parasympathetic tone and represents the basis for the ANI algorithm, is practically unchanged between 3 and 18 years old.[10,29] Nevertheless, the clinical advantages of the use of an intraoperative nociception monitor, already evidenced in adults – namely increased hemodynamic stability, reduction of intra and postoperative opioids and improved postoperative analgesia –, still need confirmation in children[24].

Regarding postoperative management, ANI usage revealed a significant correlation with pain assessed by self and hetero-assessment scales, so it can be a valuable tool. In fact, the application of subjective evaluation pain scales can be challenging, as younger children usually present some difficulty in expressing their pain and its intensity, either because of communication weaknesses or because they are not always able to distinguish between pain, affection or fear[30]. Additionally, children usually tend to only use the extremes of self-evaluation scales, as if they were dichotomic, and it is not infrequent for them to attribute different pain classifications when questioned by different people[17,30]. Therefore, by providing an objective and continuous pain evaluation, ANI presents a large potential to improve postoperative pain monitoring in children.

Finally, it is important to remember that ANI values might be influenced by other factors and may be considered not interpretable, namely in the presence of arrhythmias, apnea, irregular breathing (as when talking, smiling or coughing), pacemaker, cardiac transplant, drugs affecting the sinus node, among others.[11,20]

Case Series

The clinical case series presented below includes 5 children, aged between 3 and 9 years old, 3 females and 2 males, who underwent pediatric otolaryngology surgical procedures. HR, SBP, DBP and MBP values were recorded at constant intervals during each surgery and the value displayed on the ANI monitor was recorded every second. As observational clinical cases, nociception and pain management were guided by the traditional parameters (hemodynamic changes) and not by ANI values.

In the clinical cases presented, we aimed to assess the effect of opioid analgesic boluses on the ANI value and hemodynamic parameters, comparing them 5 and 10 minutes after drug administration. Additionally, we intended to evaluate whether there was a correlation between the self- or hetero-assessment pain scales and the values displayed by ANI during the postoperative period at PACU.

Case 1

Female, 6 years old, 20 kg, ASA-PS 2, underwent adenotonsillectomy and bilateral myringotomy. Figure 4 shows the variation in ANI values during the child's time in the OR.

First administration of fentanyl:

After the beginning of surgery, an initial dose of 1mcg/kg of fentanyl was administered and, 5 minutes later, ANI_i value increased from 41 to 59, accompanied by a decrease in HR (from 104 to 102bpm) and an increase in MBP by 5mmHg. Ten minutes later, the ANI_i value had increased to 76 while the HR decreased to 100bpm, and the MBP remained unchanged.

Second administration of fentanyl:

The baseline ANI value was 59, HR was 102bpm and MBP was 74mmHg. 5 minutes after the administration, ANI_i increased to 76, while HR decreased to 99bpm. MBP remained constant. 10 minutes after the second administration, ANI_i value decreased to 52, which was followed by a slight increase in HR to 100bpm. MBP increased from 74 to 77mmHg.

Third administration of fentanyl:

By the time of the third and final administration of fentanyl in this surgery, the ANI_i, HR and MBP values were 37, 105bpm and 78mmHg, respectively. 5 minutes later, there was an increase in the

ANI value (from 37 to 58) and a drop in HR to 99bpm. MBP increased by 2mmHg. 10 minutes after the opioid bolus, ANI value was 72, HR was 100bpm and MBP was 82mmHg.

After analyzing the data recorded by the monitor, it was noted that, during this surgery, 39.5% of the ANI_i values presented were within the ideal range (50-70). The three fentanyl intraoperative bolus were of 1mcg/kg.

At PACU, the child scored 0 on the Pediatric Anesthesia Emergence Delirium (PAED) scale (Table VI), showing no signs of emergence delirium. She was asked to rate her pain using the Wong-Baker Faces scale and selected face 4 (Figure 1), equivalent to being in a lot of pain, leading to the administration of 0.5mcg/kg of fentanyl. At the time, the minimum value displayed by the ANI monitor was 45. In the next assessment, 20 minutes later, she chose face 0, showing complete pain resolution and 90 was the value displayed by the monitor.

<u>Case 2</u>

Male, 9 years old, 36 kg, ASA-PS 2, underwent adenotonsillectomy. The ANI values are shown in Figure 5.

First administration of fentanyl:

When fentanyl was first administered (1.5mcg/kg), baseline ANI_i, HR and MBP values were 86, 116 bpm and 79 mmHg, respectively.

5 minutes later, the ANI decreased considerably to 34, while HR increased by 3 bpm and MBP fell to 74mmHg. It should be noted that endotracheal intubation took place 4 minutes after the fentanyl administration, so 1 minute before this data. 10 minutes later, the ANI_i value remained at 34, with HR and MBP increasing to 125 bpm and 95mmHg, respectively.

Second administration of fentanyl:

5 minutes after the second administration, ANI had increased from 27 to 54 and the HR decreased from 115bpm to 111bpm, with no record of the MBP value in this time interval. In the following 10 minutes, the ANI, HR and MBP values were, in that order, 42, 118bpm, and 97mmHg.

29% of the ANI_i values recorded during this surgery were within the ideal range (50-70).

At PACU, according to the PAED scale, the child presented emergence delirium - 12 points at PAED scale - so it wasn't possible to ask him to self-assess his pain, however, ANI_i was above 50. A few minutes later, the patient rated his pain 5/10 using the Numerical Rating Scale. After being given fentanyl 1mcg/kg, his pain rating decreased to 0/10, and the ANI values were consistent with sufficient analgesia (ANI_i>60).

Case 3

Male, 3 years old, 16kg, ASA 2, underwent adenotonsillectomy. Figure 6 shows the ANI values for this clinical case.

First administration of fentanyl:

When the first and only administration of 1.5mcg/kg of fentanyl took place, the ANI_i was 35 and HR was 132bpm, with no MBP being recorded. 5 minutes later, the ANI had progressed to 70, which was accompanied by a reduction in HR to 102bpm. After 10 minutes, ANI_i value was 61 and HR was 105bpm.

During the surgery, 48% of the ANI_i values were within the 50-70 range.

At PACU, he scored 15 on the PAED scale, so it was not possible to use pain self-assessment methods during the emergence delirium event. Using the FLACC scale, he was evaluated with 5 points. ANI_i values were lower than 50. He was medicated with fentanyl 1mcg/kg, with ANI_i values above 50 a few minutes later.

Case 4

Female, 7 years old, 27kg, ASA-PS 2, submitted to adenotonsillectomy. The values recorded by the ANI monitor are shown in Figure 7.

First administration of fentanyl:

Before the first administration, ANI_i was 54 and HR was 101bpm. 5 minutes later, and after endotracheal intubation, ANI was lower (51) and HR reduced to 86bm, with a MBP of 72mmHg. 10 minutes after the administration, ANI_i, HR and MBP values were 51, 122bpm and 95mmHg.

Second administration of fentanyl:

When the surgery began, a dose of 1mcg/kg of fentanyl was administered. At that time, ANI_i was 35, HR was 125bpm and MBP was 96mmHg. 5 minutes later, ANI_i was 32 and HR 114bpm. After 10 minutes, the ANI was 58 and the HR had risen to 117bpm.d

During this surgery, only 10.8% of the ANI_i values were within the ideal range (50-70).

At PACU, in the first few minutes, the child chose the face 5 of the Wong-Baker Faces scale (Figure 1), equivalent to maximum pain, showing a value of 35 on the ANI monitor. Consequently, she was given fentanyl 1mcg/kg, and, around 10 minutes later, she self-assessed her pain as face 0 on the aforementioned scale. At that point she had a value of 75 on the ANI monitor, suggesting sufficient analgesia.

Caso 5

Female, 6 years old, 18kg, ASA 1, undergoing otoplasty. Figure 8 shows the ANI values for this case.

First administration of fentanyl:

The first administration of 1.5mcg/kg of fentanyl was not associated with a significant change in HR: it went from 118bpm to 117bpm. It was not possible to compare the variation in this hemodynamic parameter with ANI value since monitor recordings only started a few minutes later.

Second administration of fentanyl:

In the second administration, after surgical incision, fentanyl was associated with an increase in ANI_i (from 35 to 50) and a decline in hemodynamic parameters, with HR falling from 127bpm to 105bpm and MBP from 76 to 58mmHg. 10 minutes later, ANI, HR and MBP were 56, 102bpm and 63mmHg.

Third administration of fentanyl:

The last administration of fentanyl resulted in a slight reduction in HR (108 to 104bpm) and MBP (58 to 56mmHg), as well as a reduction in ANI_i, which went from 51 to 44. After 10 minutes, ANI_i was 74, while HR and MBP did not change significantly, standing at 104bpm and 57mmHg, respectively.

During this surgery, 32% of ANI values were within the ideal range (50-70).

At PACU, the child self-assessed her pain with the face 0 of the Wong-Baker Faces Scale, showing consistently high ANI_i values, always above 80. She did not take any medication at PACU.

Case Discussion

One of the purposes of presenting these clinical cases was to allow a comparison between the ANI monitor and hemodynamic parameters. According to the existing literature, it is expected that analgesia increases ANI value and reduces HR and BP. In fact, the values recorded in the majority of surgeries demonstrated a negative correlation between ANI and HR variation, which evolved in opposite directions. MBP, in turn, did not follow the expected pattern on several occasions, proving to be a worse indicator than HR.

The clinical cases presented describe 10 instances of intraoperative fentanyl administration. Out of these administrations, 4 of them did not increase ANI after 5 minutes. It is noteworthy that, when the pre-opioid ANI_i was below 50 (indicating nociception), there were only 2 recorded instances in which the medication did not raise the ANI above 50 within 5 minutes. When evaluating the values 10 minutes after the drug was administered, there were also only 2 instances in which the ANI was not above 50.

Bearing in mind that, unlike ANI values, which were recorded continuously, the hemodynamic parameters were only recorded at specific time intervals, it is not possible to determine which of the two tools reflected the response to opioids first. However, it should be noted that there was only one instance where HR did not decrease 5 minutes after the administration of fentanyl, so considering those cases, HR seemed a faster indicator of analgesia than ANI.

Regarding the use of ANI in the PACU, there seems to be a correlation between the intensity of pain reported by self- and hetero-assessment scales and ANI values. It was found that children who reported having more pain had lower ANI values, while higher ANI values were found in those who reported that their pain had resolved. However, it is important to note that ANI values above 70, which is the upper limit of the ideal range, were frequently displayed when the children reported sufficient analgesia. Since the 50-70 range was originally designed to be used in anesthetized people, there is a need to determine if the threshold for adequate analgesia in conscious people is higher.

Based on the analysis of the ANI_i values during surgery and the self-and/or hetero-assessment carried out at PACU, the potential of ANI to predict postoperative pain is dubious. On the one hand, the child in clinical case 4 had the lowest percentage of ANI_i values in the ideal range (10.8%) and reported the highest pain score in the postoperative period. On the other hand, the child in clinical case 3 had the highest percentage of ANI_i values between 50 and 70 (48%), however, he experienced emergency delirium at PACU, and his pain was rated as moderate. Similarly, the child in case 5, who reported less pain in the postoperative period and had higher ANI values at PACU, had only 32% of the values at the target range during surgery, while the child in case 1 had a higher percentage - 39.5% - and reported having a higher pain score at PACU.

Considering all this information, it should be noted that, since the study population included only 5 children and in all the surgeries the opioid chosen was fentanyl, the results may not be an accurate representation of how the general pediatric population responds to opioids. Furthermore, the fact that they had all undergone otolaryngology surgeries, the majority of which were adenotonsillectomies, makes it plausible to admit the existence of a selection bias. Finally, it should also be mentioned that factors such as inter-individual sensitivity to opioids and possible reading errors may explain why opioids did not always lead to an increase in ANI.

Conclusion

In summary, ANI is a non-invasive monitoring tool that analyzes heart rate respiratory variations to assess nociception levels. It displays a value between 0 and 100, reflecting the variability in the parasympathetic tone. ANI was designed to assess nociception in the OR and, in pediatric patients, it has proven to have a significant diagnostic value in detecting nociceptive stimuli, insufficient antinociception, and re-establishment of analgesia, showing not only a correlation with the hemodynamic parameters traditionally used, but also greater sensitivity and specificity. ANI_i and DeltaANI seem to be the most reliable parameters.

The intraoperative use of ANI is emerging as a significant improvement in the management of nociception during surgical procedures. By continuously providing a measure of nociception, it allows for personalized analgesia based on individual patient response, thereby avoiding excessive or insufficient administration of opioids.

In the Post-Anesthetic Care Unit, the results obtained are also encouraging, as they have already demonstrated the existence of a correlation between ANI and the self- and hetero-assessment scales routinely used. The clinical cases presented in this dissertation have reinforced this correlation. Thus, the existing data suggests that ANI may be useful in children who are unable to report their pain, namely children who have not yet mastered verbal communication or children with cognitive deficits.

Despite the promising results, future research is needed to widely use this monitor in clinical practice. In fact, the available literature on the applicability of ANI in pediatric population remains scarce and the limited number of studies on the use of this tool in children, as well as the small sample sizes studied, make it difficult to generalize the results to a larger scale.

Further studies are required to determine the optimal use of ANI in pediatrics and establish clinical guidelines for its use. Additionally, studies are needed to clarify the benefits of ANI in minimizing the negative effects of excessive or insufficient opioid consumption, post-operative benefits, and long-term clinical outcomes. It would also be helpful to carry out a trial aimed at comparing the various nociception monitors validated for the pediatric population.

In conclusion, the use of ANI in pediatric settings has the potential to represent a significant advance in pain and nociception management. Therefore, continued attention and investment in future research are necessary to improve its practical application.

Appendix

Table I: Neonatal Infant Pain Scale (NIPS)[31]

Facial Expression	0 1	Relaxed Grimace
Cry	0 1 2	No cry Whimper (mild moaning or intermittent) Vigorous crying or silent cry (based on facial movements if intubated)
Breathing pattern	0 1	Relaxed Change in breathing (irregular, increased, gagging, breath holding)
Arms	0 1	Relaxed Flexed/extended (tense straight arms, rigid and/or rapid extension)
Legs	0 1	Relaxed Flexed/extended (tense straight legs, rigid and/or rapid extension)
State of arousal	0 1	Sleeping/awake (quiet, peaceful, settled) Fussy (alert, restless, and thrashing)

NIPS score interpretation: 0–1: no pain; 2: mild pain; 3–4: moderate pain; 5–7: severe pain

Table II: FACE, LEGS, ACTIVITY, CRY, CONSOLABILITY (FLACC)[32]

Criteria	**Score 0**	**Score 1**	**Score 2**
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, uninterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting, back and forth, tense	Arched, rigid or jerking
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging or being talked to, distractible	Difficult to console or comfort

Table III: FACE, LEGS, ACTIVITY, CRY, CONSOLABILITY - Revised (FLACC-R)[33]

Criteria	**Score 0**	**Score 1**	**Score 2**
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested; appears sad or worried	Frequent to constant quivering chin, clenched jaw; *distressed looking face; expression of fright or panic* **Individualised behaviour described by family:**
Legs	Normal position or relaxed; usual muscle tone and motion to arms and legs	Uneasy, restless, tense	Kicking, or legs drawn up; *marked increase in spasticity; constant tremors or jerking* **Individualised behaviour described by family:**
Activity	Lying quietly, normal position, moves easily; regular rhythmic breaths (respiration)	Squirming, shifting, back and forth, tense or guarded movements; mildly agitated (head back and forth, aggression); shallow, splinting breaths (respirations); occasional sighs	Arched, rigid or jerking; *severe agitation; head banging; shivering (not rigors); breath holding, gasping, or sharp intake of breaths; severe splinting* **Individualised behaviour described by family**:
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaint; occasional verbal outburst or grunt	Crying steadily, screams or sobs, frequent complaints; *repeated outbursts; constant grunting* **Individualised behaviour described by family:**
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or "talking to"; Can be distracted	Difficult to console or comfort; *pushing away caregiver; resisting care or comfort measures* **Individualised behaviour described by family:**

Table IV: Inclusion and exclusion criteria

Inclusion and exclusion criteria for articles in the systematic review
Inclusion criteria: • Studies in English language • Studies published between January 2018 and January 2024 • Studies that explore the use of ANI as a nociception monitor in pediatric patients • Studies comparing ANI with other nociception indices or studies about other nociception indices, as long as they mention ANI
Exclusion criteria: • Studies written in a non-English language • Duplicate studies • Studies including only adult population • Studies about the use of ANI in the Pediatric Intensive Care Unit

Table V: General characteristics of included studies

Authors and year of publication	Study Design	Characteristics of Participants	Primary outcome	Results
Sharma P et al. (2023)	Prospective observational study	14 children aged between 2 and 12, undergoing elective craniotomies	Evaluate the correlation between ANI and FLACC-R scale for predicting acute postoperative pain in pediatric population, undergoing elective craniotomies, comparing changes in ANI values with hemodynamic parameters and SPI	There was a strong, statistically significant, negative correlation between ANI_i and ANI_m and FLACC-R scale ($r=-0.89$, $P<0.001$ and $r= -0.88$, $P< 0.001$, respectively), during stay in the PACU. The correlation between BP and FLACC-R, although also statistically significant, was moderate ($r = 0.74$, $P<0.001$)
Chemam S et al. (2023)	Prospective experimental study	30 children aged between 5 and 12, undergoing elective surgery under general anesthesia with sevoflurane and alfentanil	Assess the impact of tetanic stimuli of varying intensities on NOL, ANI, HR and BP	The stimuli triggered an increase in NOL ($p<0.05$) and a reduction in ANI ($p<0.001$), with NOL response being influenced by the intensity of the stimulus ($p<0.001$). BP and HR remained practically unchanged

Tiryaki Ö et al. (2022)	Prospective observational study	13 adolescents aged between 12 and 17, who underwent laparoscopic appendectomy	Evaluate the applicability of ANI as a postoperative pain monitoring tool and compare it with traditional scales (FLACC, Wong-Baker Faces Pain Rating Scale and Numerical Rating Scale)	There was a statistically significant difference between the measurement averages of the pain scales ($p<0.05$) and a statistically significant negative relationship between ANI and the pain scales ($r=-0.837$, $p<0.05$ for FLACC, $r=-0.669$ for Numerical Rating Scale, $r=-0.711$ and $p<0.01$ for Wong-Baker). ANI can be used safely in the objective assessment of postoperative pain in this population
Evrard B et al. (2022)	Prospective experimental study	89 children between 2 and 7 years old, who underwent tonsillectomy	Assessing the prognostic significance of ANI and videopupillometry, measured at the end of the surgery, on morphine consumption, determined by a FLACC scale score>3 at PACU	Neither ANI nor videopupillometry measured at the end of the surgery predicted morphine consumption in the PACU (AUROC= 0.54, 95% CI [0.42-0.65], and P=0.57; and 0.52, 95% CI [0.41-0.63], and P=0.69, respectively)

Julien-Marsollier F et al. (2018)	Prospective experimental study	49 children aged between 2 and 12 years old, undergoing otolaryngology, abdominal, urological, or orthopedic surgery involving incision or laparoscopic trocar placement	Assessing the usefulness of ANI in detecting surgical stimuli in children	ANI had diagnostic value for detecting surgical stimuli in children: AUROC 0.755 (0.73-0.772), 0.771 (0.755-0.787), and 0.756 (0.738-0.774) for ANI_i, ANI_m, and DeltaANI, respectively
Weber F et al (2018)	Prospective observational study	131 children between the ages of 2 and 12, undergoing elective surgery under sevoflurane anesthesia	Evaluating the ability of ANI to detect inadequate antinociception	In patients with ANI_i<50, values returned to ±60 within 2 minutes after fentanyl administration (ANI_m and HR values remained unchanged). In patients with ANI_i>50, opioids did not affect ANI or HR.

Table V: General characteristics of the narrative reviews selected

Author and year of publication	Number of studies included	Purpose of Review	Results/findings
Nada Sabourdin and Isabelle Constant (2023)	*Not mentioned*	Describe the pediatric data available about nociception monitors	SPI, Analgesia-Nociception Index (ANI), and pupillometry may be valuable tools to evaluate intraoperative nociception across various age groups within the pediatric population
Gianluca Bertolizio, Marta Garbin and Pablo M. Ingelmo (2023)	*Not mentioned*	Review the nociception monitors available in pediatric clinical practice	All available monitors show some sort of limitations (HRV-based monitors are influenced by drugs like inotropes and aren't suitable for cardiac surgeries; pupillometry is affected by certain drugs) so they may have limited use in critically ill children. Pupillometry and ANI/NIPE present potential advantages over alternative monitoring methods, with pupillometry being more sensible and less medication-dependent and ANI/NIPE being user-friendly and more specific. Skin conductance did not show promising results. The use of intraoperative nociception monitors, in addition to HR and BP, to guide anesthesia, should be encouraged.
Byung Gun Lim (2019)	30 studies	Evaluate the effectiveness of various nociception monitoring devices in pediatric intraoperative pain management during general anesthesia	ANI and NIPE have shown promising results. ANI has exhibited better efficacy on postoperative pain than the other monitors. There is little evidence that SCA allows for monitoring analgesia during general anesthesia in pediatric patients. Pupillometry may be associated with inaccurate or complicated measurements.

			SPI, ANI, and pupillometry could be valuable tools for assessing the impact of regional analgesia administered during general anesthesia.
Saranya Devi Subramaniam *et al.* (2018)	*Not mentioned*	Explored different physiological and behavioral pain assessment techniques	Looking solely at physiological signals to evaluate pain is still not an ideal approach, as it can be directly influenced by medication, underlying health conditions, treatments, fear, and the emotional state of the individuals involved.

Table VII: PAED (Pediatric Anesthesia Emergence Delirium) Scale[34]

Delirium Symptom	**Not at all**	**Just a little**	**Quite a bit**	**Very much**	**Extremely**
Child makes eye contact with the caregiver	4	3	2	1	0
Child's actions are purposeful	4	3	2	1	0
Child is aware of his/her surroundings	4	3	2	1	0
Child is restless	0	1	2	3	4
Child is inconsolable	0	1	2	3	4

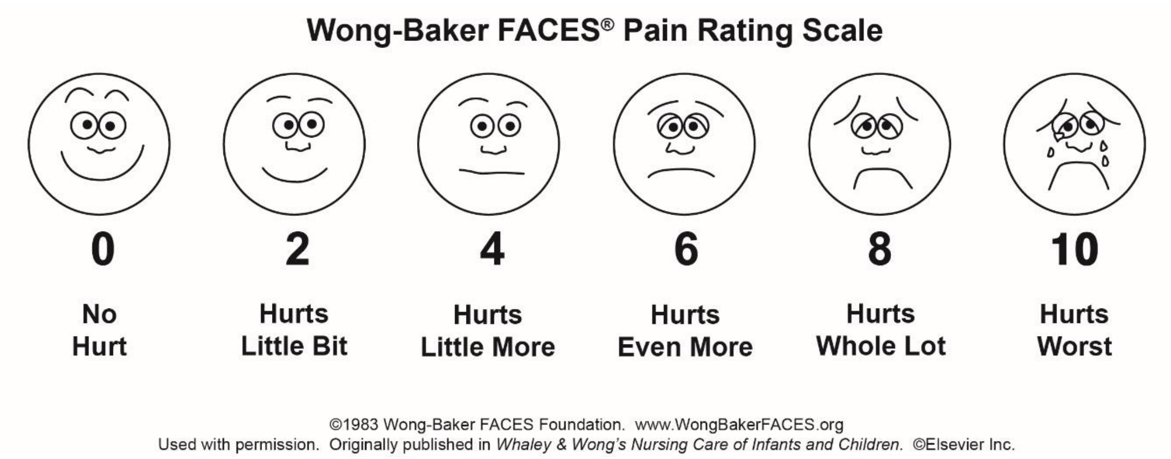

Figure 1: Wong-Baker FACES Pain Rating Scale – Used with permission[35]

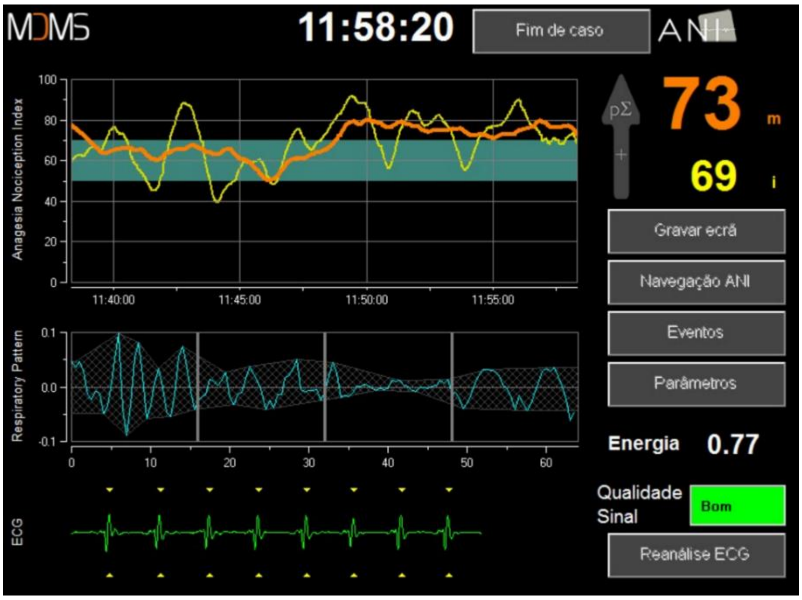

Figure 2: ANI Monitor screen (screenshot during clinical case)

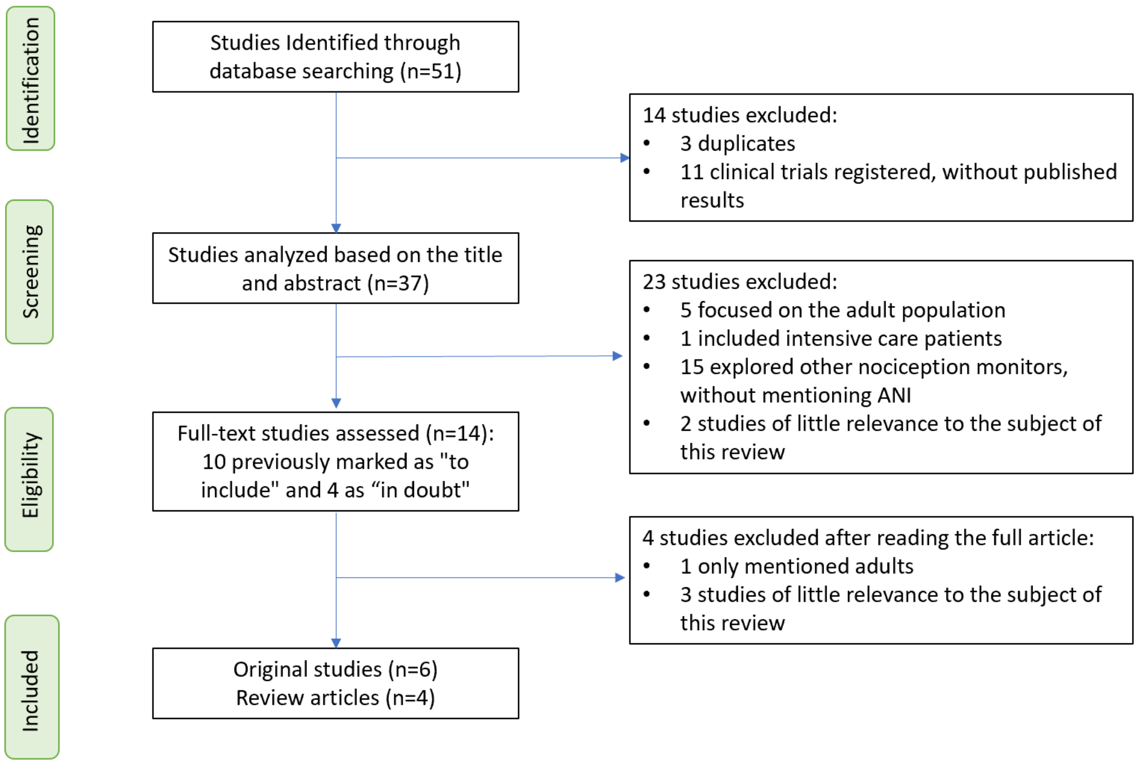

Figure 3: PRISMA Flow Diagram for article search and selection

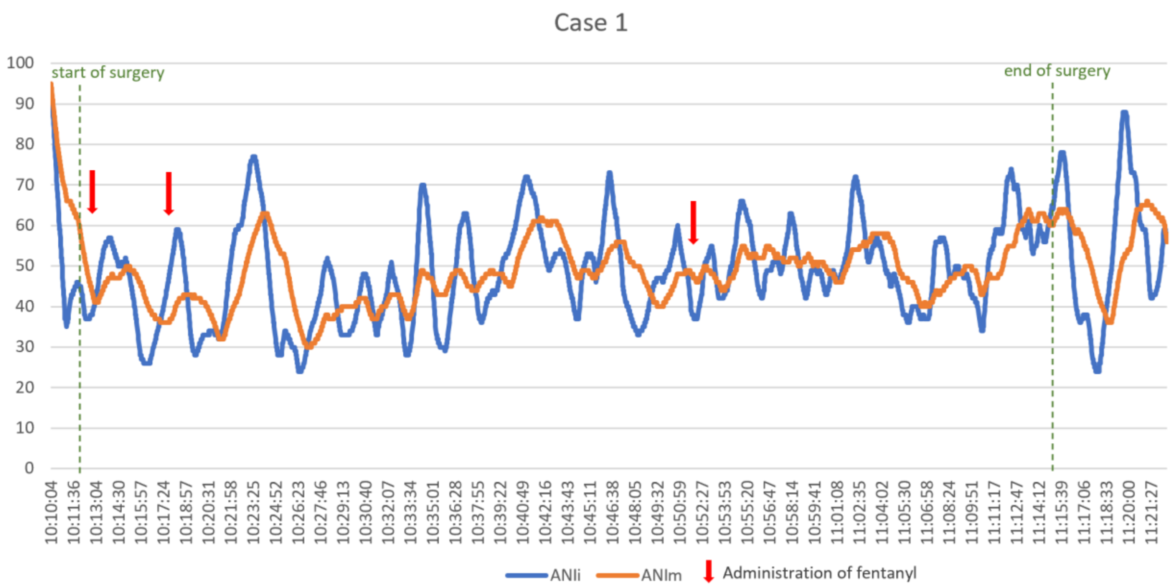

Figure 4: Case 1 – ANI values exhibited during the case, OR

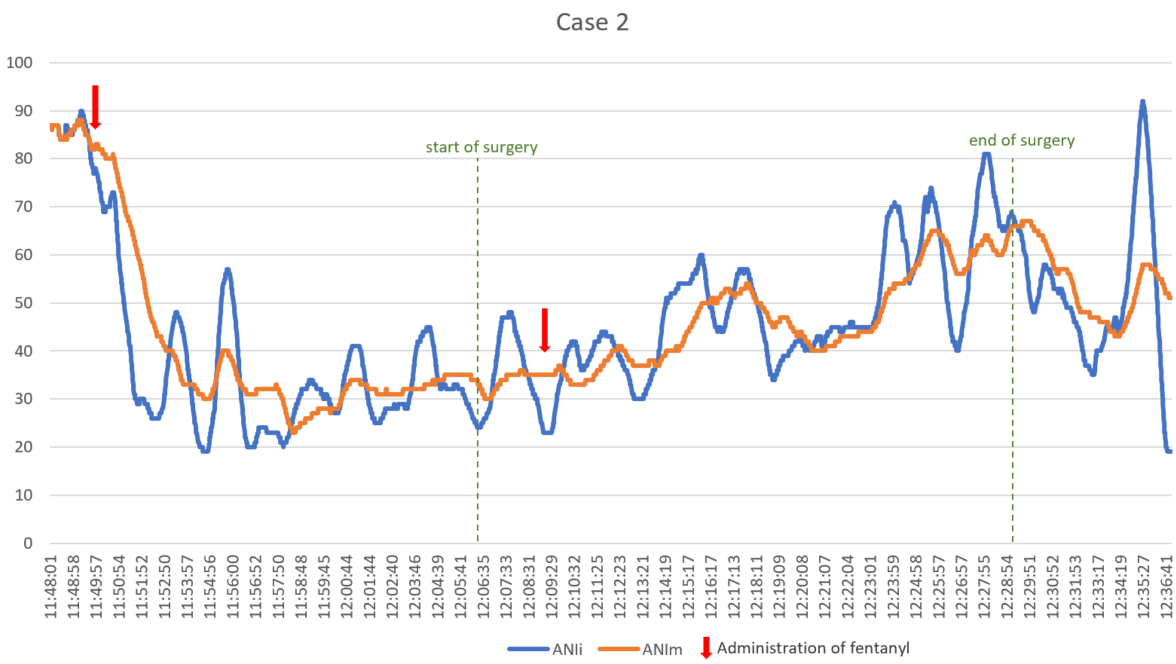

Figure 5: Case 2 – ANI values exhibited during the case, OR

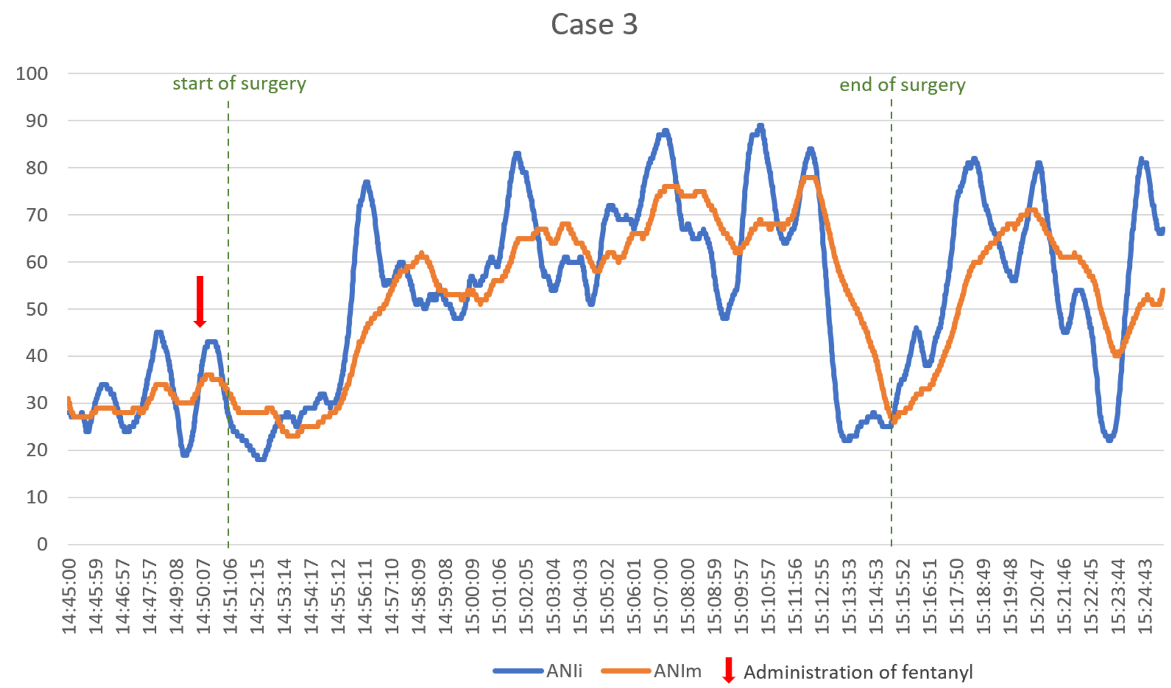

Figure 6: Case 3 – ANI values exhibited during the case, OR

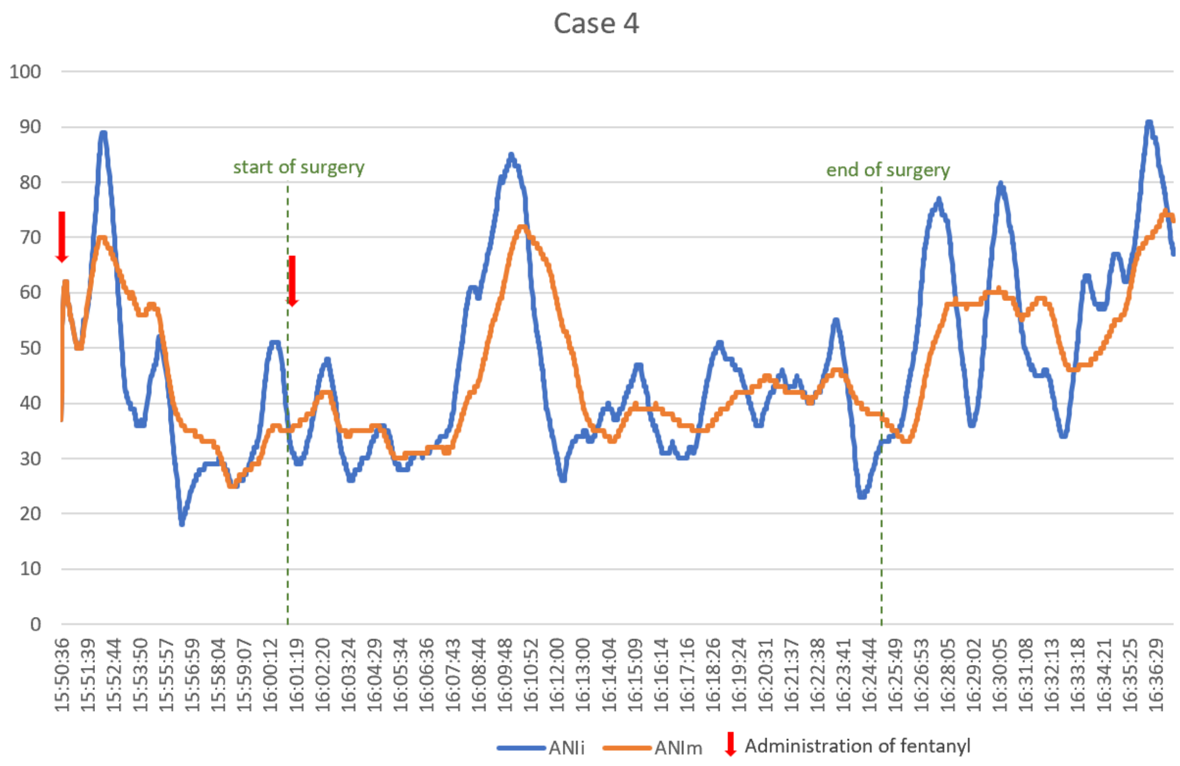

Figure 7: Case 4 – ANI values exhibited during the case, OR

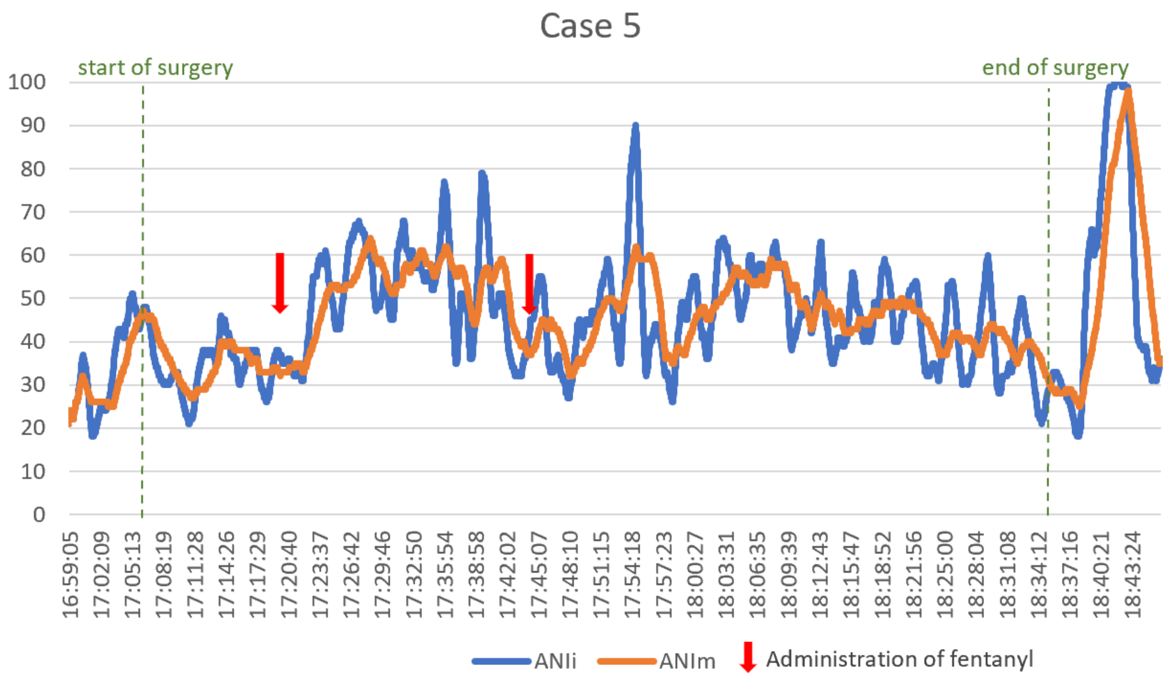

Figure 8: Case 5 – ANI values exhibited during the case, OR

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