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Monitoring brain activity using Pediatric Sedation State Scale, Patient State Index and Near-Infrared Spectroscopy during procedural sedoanalgesia in pediatric patients

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Summary

LIST OF ABBREVIATIONS

PSA: Procedural Sedation, Anxiolysis, and Analgesia

NIRS: Near Infra-Red Spectroscopy

PSI: patient state index

BIS: Bispectral Index

PSSS: Pediatric Sedation State Scale

fMRI: functional MRI

EEG: Electroencephalography

PET: Positron Emission Tomography

HbH: Deoxyhaemoglobin

HbO2: Oxyhaemoglobin

HbT: Total Haemoglobin

rSO2: Regional Oxygen Saturation

c-rSO2: Cerebral Oxygen Saturation

NIBP: non-invasive Blood Pressure

SpO2: Peripheral Oxygen Saturation

HR: Heart Rate

RR: Respiratory Rate

EtCO2: End Tidal CO2

FNT: Fentanyl

PPF: Propofol

KET: Ketamine

MDZ: Midazolam

PICU: Pediatric Intensive Care Unit

ABSTRACT

Pediatric patients frequently require painful and invasive procedures as part of their diagnostic and therapeutic treatment.

The aim of our study was to evaluate different scales to monitor cerebral activity, namely Pediatric Sedation State Scale (PSSS), Patient State Index (PSI) and Near-Infrared Spectroscopy (NIRS) to identify their usefulness and reliability during sedoanalgesia in pediatric patients.

Thirty-five patients were included in our study and underwent 77 sedo-analgesia sessions. Overall, 90 painful or invasive procedures were performed. Subgroups treated with the combination of ketamine and propofol (KET+PPF) and Fentanyl and Propofol (FNT+PPF) were compared.

Administration of a single bolus of PPF significantly reduced PSI >5% in 66.7% of cases. Instead, KET and FNT did not influence PSI. Interestingly, a PSI < 70 correlated with reduced perception of the painful stimulus. The combination of FNT+PPF was more frequently associated to PSI values between 30 and 70, as well as to lower PSI values (<70) compared to KET+PPF (p=<0.001, p=<0.001). We did not observe significant variations in NIRS values during the procedure.

In our study, we observed that all the scales may give specific information from different points of view. PSSS is a behavioral scale which gave information about safety and adequacy of sedation. PSI

was altered by the administration of drugs and the application of noxious stimuli, reflecting patient's state of consciousness. NIRS technology reflects brain oxygenation, and in our study testified that no dangerous cerebral desaturation happened.

INTRODUCTION

Pediatric patients frequently require painful and invasive procedures as part of their diagnostic and therapeutic treatment[1]. Since the cumulative effects of these painful experiences can lead to adverse psychological outcomes for children and their families, avoid pain is crucial[2].

In the last decade, numerous international[3-6] guidelines highlight how procedural sedation should be safe, but also effective and personalized.

The definition of "Pediatric procedural sedation (PPS)" encompasses all the techniques and medications utilized to reduce anxiety and pain associated with unpleasant or painful procedures, such as analgesia, anxiolysis, and sedation[7].

In the pediatric population, PPS is not only confined to major painful procedures, but can be performed for routine events as laceration repairs, IV cannulation, lumbar puncture, fracture reduction, thoracentesis, bone marrow aspirations and biopsy, gastrointestinal endoscopy, among others. Furthermore, other non-painful diagnostic procedures, such as radiological examinations that require the child to remain still, may require some level of sedation for younger patients.[7,8].

Adequate pain and anxiety control could be easy reached in a deep sedation state, but deep sedation may be associated with depression of protective airway reflexes, respiration and cardiovascular system. For these reasons, appropriate drug selection for the planned procedure and the specific patient is necessary[9].

The optimal level of procedural sedation in children is the result of a balance between optimal symptoms control and sedation depth[4]. During each stage of the medical procedure, pain assessment must be conducted regularly to assess the need for pharmacological and/or non-pharmacological interventions.

The ideal procedural sedation scale should measure a variety of factors, such as control of movement, stress and pain, while at the same time allowing for categorization of respiratory depression or other effects related to sedation[10]. Nowadays, the evaluation of sedoanalgesia in pediatric population is based on vitals parameters and behavioral scores. However, vital signs may change because of clinical and pharmaceutical conditions, and behavior observation could be useless in critically ill patients[11].

Despite improvements in pediatric pain management, rates of pain perception remain high[12].

1.1 PHARMACOLOGIC AGENTS

To date, European guidelines suggest a variety of pharmacologic agents to be used to obtain a safe and efficient sedation (*Table I*).

Table I: Overview of current pharmacological choices for procedural sedation

Agent	**Ketamine (dissociative anesthetic)**
Initial IV dose	1 to 2 mg/kg; for healthy patients without QT prolongation or receiving medications that prolong the QT interval, premedication with ondansetron 0.15 mg/kg IV (maximum dose 4 mg) is recommended
Repeat IV dose (as needed)	0.5 to 1 mg/kg; repeat every 5 to 10 minutes, titrating to desired level of sedation
Onset (minutes)	1 to 2
Duration (minutes)	15 to 30
Additional notes	**Properties**: provides sedation and analgesia for moderately to severely painful procedures. **Adverse effects**: vomiting and emergence reactions are common. Laryngospasm and apnea occur rarely, but bag mask ventilation may be necessary in about 1% of sedations. Co-administration of anticholinergics, propofol, or barbiturates increases the risk of serious adverse events. **Relative contraindications and precautions**: age younger than 12 months, active pulmonary infections (including URI), known or suspected cardiac disease, suspected increased intracranial pressure (e.g. intracranial mass or obstructive

	hydrocephalus), glaucoma or acute eye injury (open globe), porphyria, thyroid disease, or seizures. **Absolute contraindications**: age younger than 3 months or patients with known or suspected psychosis
Agent	**Propofol (sedative-hypnotic anesthetic)**
Initial IV dose	Initiate infusion at 150 mcg/kg per minute and titrate gradually to response (up to 250 mcg/kg per minute) or 6 months to 2 years of age: 2 mg/kg IV bolus dose 2 years of age and older: 1 to 1.5 mg/kg IV bolus dose
Repeat IV dose (as needed)	Not applicable for continuous IV infusion; titrate infusion rate as needed or Additional IV bolus dose 0.5 mg/kg every 3 to 5 minutes, titrating as needed up to 3 mg/kg. Wait at least 3 to 5 minutes between doses to assess effect
Onset (minutes)	≤0.5
Duration (minutes)	5 to 15 after single bolus dose, longer after prolonged infusion or when repeated bolus doses are given
Additional notes	**Properties**: provides deep sedation but can produce general anesthesia, especially with multiple bolus doses or high continuous infusion rate. It does not provide analgesia: for painful procedures, an analgesic agent (eg, ketamine, fentanyl), regional anesthetic, or local anesthetic should be co-administered. Commonly used for diagnostic imaging (CT, MRI). Causes peripheral injection-site pain. Rapid onset of sedation with good neurologic recovery. Reduces intracranial pressure. **Adverse effects**: respiratory depression, oxygen desaturation, apnea, hypotension, and/or rapid transition to deeper levels of

	sedation, especially with overly rapid administration of bolus injection. **Absolute contraindications**: porphyria, cardiac compromise
Agent	**Ketamine and propofol (also known as ketofol)**
Initial IV dose	Ketamine 0.5 mg/kg bolus followed by propofol 0.5 mg/kg. As propofol may reduce the risk of vomiting caused by ketamine, premedication with ondansetron may not be required.
Repeat IV dose (as needed)	Propofol 0.5 mg/kg every 2 minutes, as needed or Ketamine 0.5 to 1 mg/kg every 10 minutes
Onset (minutes)	<1
Duration (minutes)	15 to 30
Additional notes	**Properties**: may be administered simultaneously in the same syringe. Optimal dosing has not been established. Range of reported dosing is ketamine 0.2 to 1 mg/kg IV with propofol 0.5 to 2 mg/kg IV. The higher range of these doses may be indicated in patients with more painful procedures. **Adverse effects and contraindications**: as above for ketamine and propofol; in addition, combining the two drugs changes the frequency of some adverse effects: risk of apnea, laryngospasm, hypotension, and bradycardia may be higher than for patients receiving ketamine alone: risk of vomiting may be lower than for patients receiving ketamine alone; risk of bradycardia and hypotension may be lower than for patients receiving propofol alone
Agent	**Dexmedetomidine (alpha-2 agonist)**
Initial IV dose	Loading dose (dexmedetomidine alone): 1 to 2 mcg/kg over 10 minutes Maintenance continuous infusion (dexmedetomidine alone): 1 to 2 mcg/kg/hour

Repeat IV dose (as needed)	Repeat loading dose: 0.5 to 1 mcg/kg over 10 minutes. Titrate infusion rate as needed to achieve clinical effect
Onset (minutes)	5 to 10
Duration (minutes)	30 to 70
Additional notes	**Properties**: sedation and modest analgesia with minimal respiratory depression. Commonly used for diagnostic imaging (CT, MRI). **Adverse effects**: bradycardia, hypertension, or, especially with loading dose, hypotension. Rarely, upper airway obstruction, including laryngospasm. **Relative contraindications**: children who are inadequately hydrated or have reduced cardiac output. **Absolute contraindications**: dexmedetomidine should be avoided in patients receiving digoxin or other medications acting on the atrioventricular node or with cardiac conduction abnormalities (e.g. sinus node dysfunction).
Agent	**Midazolam (benzodiazepines)**
Initial IV dose	6 months to 5 years of age: 0.05 to 0.1 mg/kg IV, maximum single dose 2 mg 6 to 12 years of age: 0.025 to 0.05 mg/kg IV, maximum single dose 2 mg Over 12 years of age: 1 to 2 mg IV
Repeat IV dose (as needed)	After initial IV dose, repeat after 2 to 5 minutes, titrating to desired level of sedation as follows: 6 months to 5 years of age: 0.2 mg/kg per dose (maximum total dose 6 mg) 6 to 12 years of age: 0.1 mg/kg (maximum total dose 6 mg) Over 12 years of age: 1 to 2 mg (maximum total dose 10 mg)
Onset (minutes)	1 to 3

Duration (minutes)	15 to 60
Additional notes	**Properties**: provides sedation but no analgesia. For painful procedures, analgesic agents (e.g. ketamine, fentanyl) should be co administered. Provides amnesia, mild anxiolysis, and mild sedation for procedures not requiring full immobility (e.g. laceration repair with local topical anesthesia). When combined with fentanyl, can produce moderate or deep sedation, but less effective and more adverse respiratory events reported when compared to sedation with ketamine alone or combined with propofol. Flumazenil can reverse effects but should be avoided in patients with seizure disorder or who are chronically maintained on benzodiazepines. **Adverse effects**: respiratory depression and apnea, especially when combined with opioid medications (e.g. fentanyl); paradoxical reactions including hyperactivity, aggressive behavior, and inconsolable crying. **Contraindications**: Hypersensitivity to midazolam or any of its components.
Agent	**Morphine (opioid)**
Initial IV dose	0,1-0,2 mg/kg IV
Repeat IV dose (as needed)	0,1-0,2 mg/kg IV
Onset (onset)	20
Duration (minutes)	240
Additional notes	**Properties**: morphine is a good choice for PSA due to its ability to produce analgesia, euphoria and sedation. Its long duration may be useful if pain is anticipated after the procedure, even if I may also prolong somnolence.

	Adverse effects: nausea, feeling of warmth, heaviness of extremities, dry mouth, hypotension and pruritus, hypotension, bradycardia, vasodilation, hypoxia, depression on the ventilatory centers in brain stem **Contraindications**: morphine is excreted by kidney and could increase the risk of ventilator depression in patient with renal impairment.
Agent	**Fentanyl (opioid)**
Initial IV dose	1-2 mcg/kg
Repeat IV dose (as needed)	1 mcg/kg
Onset (minutes)	2-3
Duration (minutes)	30-60
Additional notes	**Properties**: fentanyl is a synthetic opioid agonist. It is about 100 times stronger than morphine and provides adequate analgesia for procedures with moderate to severe pain. It can also be effective when administered intranasally or via nebulizer. **Adverse reactions:** ventilatory depression, chest wall rigidity following rapid, large boluses (>15 mcg/kg), pruritus, hypoxemia, apnea.

The European Society for Pediatric Anesthesiology (ESPA) recommends different types of pharmacological approaches based on the level of pain expected[5]. Typically, painless procedures can be performed with sedation alone, while painful procedures require both analgesia and sedation. [4, 13].

A recent survey conducted by Daverio *et al*. showed that fentanyl is the first-choice opioid in Europe, followed by morphine, while midazolam is the first-choice benzodiazepine. Propofol and ketamine are reported as second-choices or in difficult sedation cases [14]. This survey underlines that best sedation is obtained by

a combination of drugs, to use different active principles to guarantee adequate pain and consciousness control. The most used drugs combination was opioids and benzodiazepines (fentanyl and midazolam). Morphine and midazolam were the second-best combination. In cases of difficult sedation, the top three drugs used were ketamine, propofol and dexmedetomidine. [14]

1. METHODS OF PAIN ASSESSMENT

Several studies tried to find an objective pain measurement, investigating directly cerebral response to pain. The experience of nociception involves multiple brain regions, termed the "pain matrix," composed of the anterior cingulate cortex, the primary and secondary somatosensory cortex, the insular cortex, the dorsolateral prefrontal cortex and the parietal cortex. However, the elaboration and encoding of pain occur in the pre-frontal cortex [11,15].

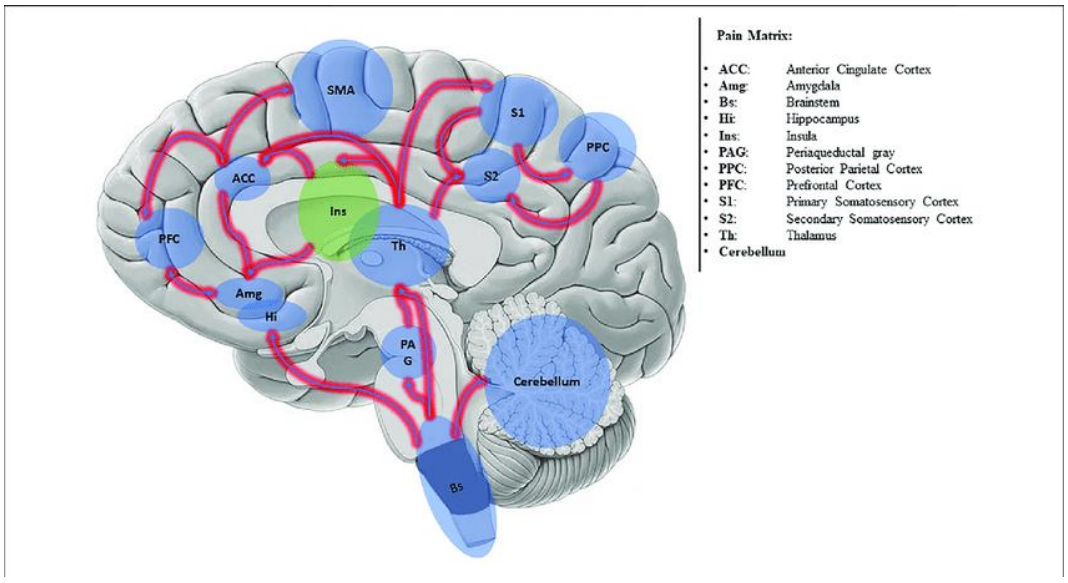


***Figure 3**:* the "pain matrix"[23]

Non-invasive neuroimaging and neurophysiological techniques, such as near infrared spectroscopy (NIRS), functional magnetic resonance imaging (fMRI), magnetoencephalography (MET), positron emission tomography (PET) and electroencephalography (EEG) have been used to explore the brain responses to acute painful procedures[16]. While EEG and MET directly analyzed neuronal

activity, NIRS, fMRI and PET detect hemodynamic changes which reflect neuronal activation[15]. fMRI and PET appear to be excellent tools to study the nociceptive pathway and cerebral response, but they are expensive and cannot be used routinely[15].

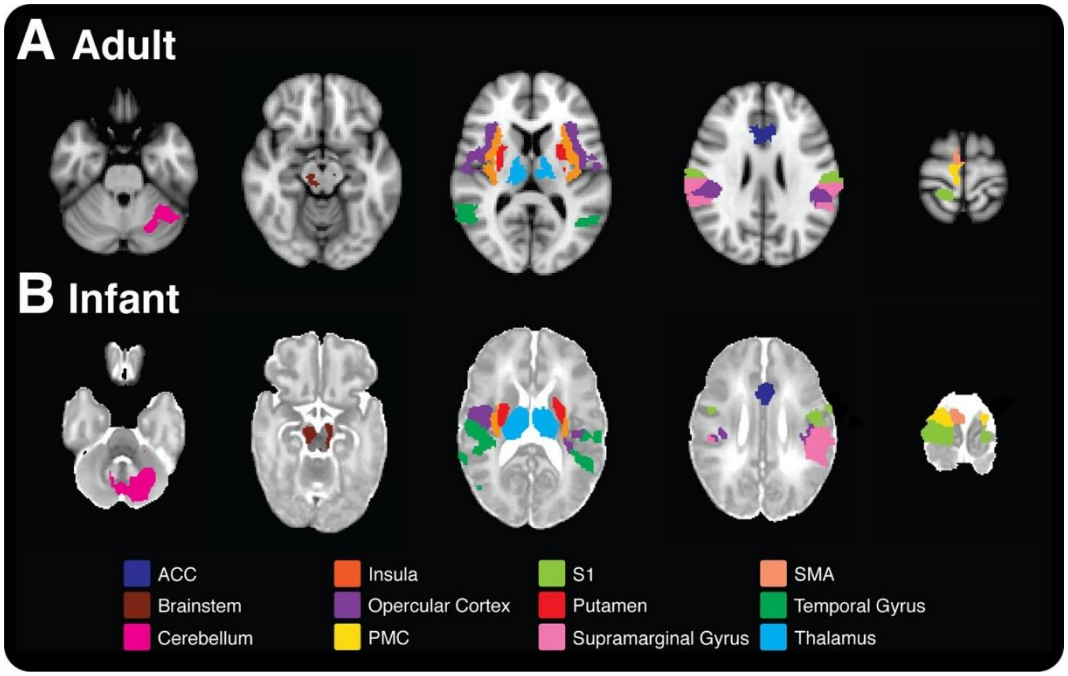


***Figure 4**:* comparison between fMRI response to pain in adults and children[14].

2.1 NIRS TECHNOLOGY

NIRS technology was introduced in 1977 by Jobsis[17]. It uses near infrared light (700-1000 nm) to measure the concentration of oxygenated hemoglobin, based on its ability to absorb light [16]. Thanks to the different absorbance spectrum, it can measure changes in the levels of oxygenated and deoxygenated hemoglobin concentrations in the blood and tissue[17-19]. It was originally developed as a device for real-time measurements of cerebral oximetry during cardiac surgery[18].

Nowadays, NIRS monitoring is a non-invasive, relatively inexpensive technique which can provide real time information at the bedside[20].

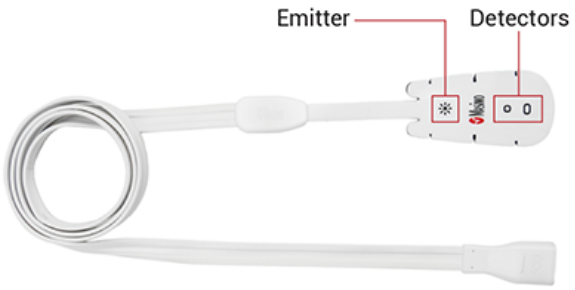


***Figure 5**:* example of a NIRS sensor[29]

2.1.1 Cerebral NIRS

The sensor is applied to the forehead area. Changes in c-rSO2 reflect changes in oxygen supply or metabolic demand[21]. Several physiological and pharmacological factors may influence c-rSO2 values[19]. Indeed, oxygen supply depends on cardiac output, blood pressure, heart rate, PaCO2 and SaO2, while metabolic demand may be influenced by clinical condition and anesthetic drugs[22].

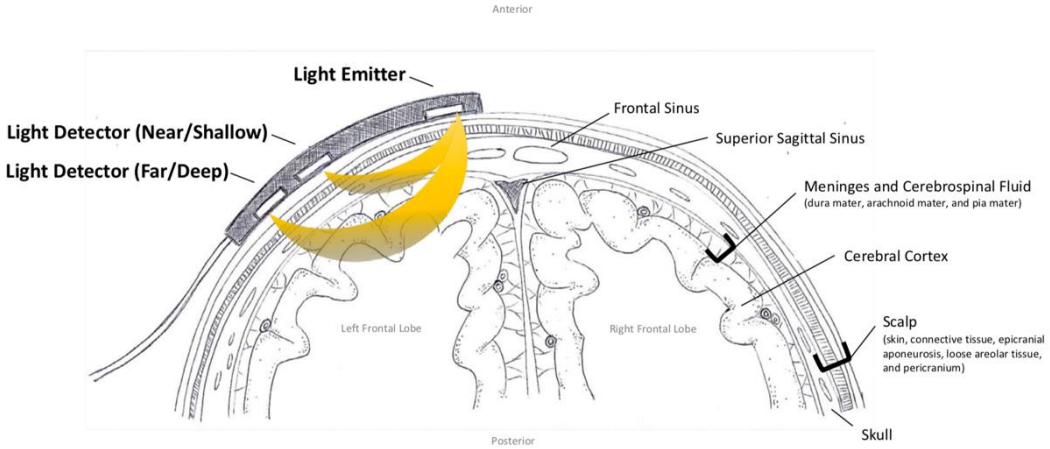


Figure 6. Cerebral Near Infrared Spectroscopy[19].

2.2 Processed EEG

In clinical practice, two different EEG-based analyses are available in addition to standard EEG (processed EEG, also known as p-EEG). They convert the EEG variables into a single index through mathematical algorithms. This index represents the level of hypnosis. Some examples of p-EEG monitors are the

Bispectral Index Monitor (BIS, Medtronic Inc.) and the Patient State Index (PSI, Masimo Inc.) of the SEDLine brain function monitor [23].

BIS. BIS looks at EEG signals and correlates a number with the depth of unconsciousness, where the lower the number, the deeper the sedation[5].

A study conducted by Gamble et al. used BIS during procedural sedation in a Pediatric ED demonstrated a high frequency of over sedation (78.5% reached general anesthesia) during most procedural sedations[24].

PSI. The PSI is an index of the depth of anesthesia calculated by the SedLine algorithm that combines multiple EEG parameters such as:

- changes in power in various EEG frequency bands;
- changes in symmetry and synchronization between critical brain regions;
- the inhibition/activation of regions of the frontal cortex[25].

PSI correlates with the patient's current sedation/anesthesia state on a scale from 0 to 100, where values over 80 apply when the patient is completely awake, whereas values under 20 indicate burst suppression. The correct general anesthesia depth is indicated by the manufacturer as a PSI value between 25 and 50. It is currently unknown if this threshold applies to children[26].

The PSI is handy in clinical practice as it allows the visualization of simple graphs, instead of complex EEG waves, providing instant and easy information on the patient's sedation status[25].

2.3 PSSS

In 2017, Cravero et al. validated the Pediatric Sedation Scale State (PSSS), that is a six-point scale to measure the effectiveness and efficiency of procedural sedation in children[10]. It monitors pain, anxiety, movement and adverse side effects through the observation of patient's behaviors. The ideal sedation state, defined as stillness and normal vital parameters, corresponds to PSSS Level 2 or 3. Over sedation is a score of 0 or 1 and under sedation is a score of 4 or 5. Adequate sedation is when the PSSS score measures 2 or 3 for at least 90% of the observation.[27] Behavioral responses to pain, that include facial actions, body movements and cry, seem to be the most sensitive and specific pain indicators in infants[16]. However, in critically ill

or sedated children the behavioral responses may be reduced by drugs as sedation or muscular blocking agents or increased by other causes of discomfort[16].

Similarly, vital parameters may be influenced by drugs effect, underlying clinical condition and any other acute event[11].

Table II: Pediatric Sedation State Scale (PSSS)

State	**Behavior**
5	Patient is moving (purposefully or not purposefully) in a manner that impedes the proceduralist and requires forceful immobilization. This includes crying or shouting during the procedure, but vocalizing is not required. Score is based on movement.
4	Moving during the procedure (awake or sedated) that requires gentle immobilization for positioning. May verbalize some discomfort or stress, but there is no crying or shouting that expresses stress or objection.
3	Expression of pain or anxiety on face (may verbalize discomfort), but not moving or impeding completion of the procedure. May require help positioning (as with a lumbar puncture) but does not require restraint to stop movement during the procedure.
2	Quiet (asleep or awake), not moving during procedure, and no frown (or brow furrow) indicating pain or anxiety. No verbalization of any complaint
1	Deeply asleep with normal vital signs, but requiring airway intervention and/or assistance (e.g. central or obstructive apnea, etc.)
0	Sedation associated with abnormal physiologic parameters that require acute intervention (i.e. oxygen desaturation<90%, blood pressure is 30% lower than baseline, bradycardia receiving therapy).

Although several pain measures exist to assess pain in infants and noncommunicative children, none have been considered a “gold standard”[16].

AIM OF THE STUDY

The aim of our study was to evaluate different scales to monitor cerebral activity, namely PSI, NIRS and PSSS, to identify their usefulness and reliability during sedoanalgesia in pediatric patients.

MATERIALS AND METHODS

1. STUDY DESIGN

We conducted a single-center exploratory observational study to analyze brain activity during procedural sedoanalgesia performed on pediatric patients, monitored by PSI, NIRS and PSSS.

2. POPULATION

Between January and August 2024, all pediatric patients referred to the Women's and Children's Hospital of Verona (Pediatric Intensive Care Unit, Pediatric Oncology or Pediatric Ward) who required procedural sedation to undergo diagnostic or therapeutic painful procedures were assessed for inclusion.

Eligibility for sedation was established according to our local departmental practice.

Children affected by central and neurodegenerative pathologies, children with deformities or devices that could forbid the adequate application of sensors on the forehead, or children undergoing emergency procedures were excluded.

3. DEFINITIONS

Session: a single procedural sedoanalgesia.

Procedure: a diagnostic or therapeutic technique performed on a patient. More procedures could occur during a single session.

Sedation starting point (t_0): in each session, sedation starting point (t_0) is defined as the moment in which the drug was injected.

Sedation ending point (t_n): in each session, sedation ending point (t_n) is defined as the moment in which electrodes of the bedside multi-parametric monitor were removed, since the patient was considered awake and no longer required monitoring.

Noxious stimulus: the stimulus that could provoke pain in an awaken patient, including puncture of the skin, bone aspirate, lumbar puncture, bone biopsy or muscle electrical stimulation.

Adverse reaction: according to SIVA definition, an adverse reaction (AEs) is defined as "Unexpected and undesirable response(s) to medication(s) and medical intervention used to facilitate procedural sedation and analgesia that threaten or cause patient injury or discomfort" [28].

4. MONITORING TOOLS AND METHODS

4.1 Near Infrared Spectroscopy device (NIRS)

NIRS was utilized to monitor cerebral activity from an oxygenation point of view. Cerebral tissue oxygenation was continuously recorded via a non-invasive NIRS-based device (O3TM device, Masimo Corporation, Irvine, CA). NIRS device has two channels, each consisting of an emitting and a receiving optode. Optodes are placed in a flexible rubber holder that prevents interference from external light sources and keeps constant at 4 cm the distance between the emitter and receiver optodes. Optodes are applied in the frontal region. The system uses NIRS, interrogating tissue by transmitting light of four different wavelengths through the tissue and processing the received light waveforms, to provide continuous measurement of rSO_2.[29]

Left and right NIRS values are instantaneously represented on the monitor device as a number (%) and as trends available as a horizontal graph. Furthermore, the device automatically and continuously calculates a number called "Dbase" which represents the difference between the user defined baseline and the current NIRS value as a percentage of the basal value.

NIRS values are recorded by the device every two seconds.

Pathological values are to be considered for an oxygenation under 60% or over 90%.

4.2 SedLine (PSI)

The SedLine system is a 4-channel electroencephalographic (EEG) monitor applied to the patient's frontal area, specifically designed for intraoperative use or intensive care. It is able to translate cerebral electrical activity into a scale, the Patient State Index (PSI), which gives information about the state of consciousness of the patient.

The PSI is a processed EEG parameter that correlates with the effect of anesthetic agents and takes into account, among others, the following factors: (1) power variations in various EEG frequency bands, (2) variations in symmetry and synchronization between critical regions of the brain, and (3) inhibition of regions in the frontal cortex. It gives immediate visual information about the depth of sedation and consciousness of the patient.

Correct values to perform a safe procedural sedation are between 30 and 70.

4.3 Behavioral scale (PSSS)

The patient was constantly observed by the operator, in order to detect behavioral changes, which were noted as a PSSS value. Table II summarizes characteristics of each PSSS value. In order to obtain a safe and efficient sedation, during a single session it is recommended that a patient should scores values of 2 or 3 at least 90% of duration of the session. Otherwise, they are considered as under sedated (PSSS values of 4 or 5) or over sedated (PSSS values of 0 or 1).

4.4 Vital parameters

Vital signs were continuously monitored by a bedside multiparametric monitor, according to our standard of care. Heart rate (HR), respiratory rate (RR), oxygen saturation by pulse oximetry (SpO2) and end tidal CO2 (EtCO2) data were recorded simultaneously with the NIRS data.

5. ETHICS

Informed parental consent was obtained in all cases.

6. STUDY PROCEDURE

According to the local standard of care, all the procedures have been conducted in a safe dedicated setting (inside or outside the PICU depending on ASA physical state) with adequate emergency equipment. Multiple procedures could be performed during the same sedoanalgesia session on a patient.

During the study protocol, the anesthesia-sedation management was standardized according to our departmental practice, adjustable by the pediatrician according to the patient's condition and anamnestic features.

Depending on the type of procedure, patient's history and clinical status, induction medications included propofol (1-2 mg/kg IV), and/or fentanyl (1ug/kg IV), and/or ketamine (0,5-2 mg/kg IV). Subsequently, by assessing the patient's respiratory rate, airway patency, muscle tone, presence of purposeful movement, the physician could administer additional boluses of drugs, such as propofol (0,5-1 mg/kg) and/or fentanyl (0,5 ug/kg IV), and/or ketamine (0,5 mg/kg), as necessary. Oral midazolam (0,5 mg/kg) was administered if patient was excessively anxious or nervous at least 15 minutes before induction of sedoanalgesia.

Preoperatively, the team leader explained the course of procedure as well as the aim of the study to the parents, to obtain their informed consent. Medical history (age, sex, weight, ASA score and underlying pathology) and type of procedure were obtained. If a patient needed multiple procedures during the study period, age and weight were updated from time to time.

The exact time of start and end of sedation, the precise time of the noxious stimulus, and any events that occurred during the study (e.g. adverse effects, need to administer medications to resolve adverse effects, etc.) were documented in the medical record of the patient. For each patient, drugs administration, type and dosage, O_2 administration via face mask were recorded. PSSS was also constantly evaluated and noted as the operator continuously observed the patient.

During the entire procedure, another physician manually recorded values of NIRS (right and left), PSI, HR, EtCO2, SpO_2, on a standardized form. In addition, HR, SpO_2, NIRS and PSI values were automatically saved by the devices, so they were available for off-line consultation after the procedure in case of missing data. Data

acquisition was always completed by the same researcher present during the procedure itself. According to the patient's state (anxious, scared or relaxed), NIRS, PSI and the other probes were placed before or after anesthesia induction, using pharmacological techniques for painful and stressful procedures (usually, premedication with midazolam).

First, SedLine system was applied on the patient's forehead midline, after skin cleaning if necessary. Second, NIRS probes were applied symmetrically on the patient's forehead, lateral to midline and to the SedLine system. The physician performing sedation could see the monitor throughout the study. All sensors remained on the forehead throughout the anesthetic period and were removed after emergence from anesthesia, excluding the case in which any dangerous adverse effect occurred. In this case, if the procedure went on, the operator continued checking vital parameters and PSSS only.

Figure 7: correct positioning of NIRS probes (laterally) and SedLine (medially)[40]

Usually, the procedure was performed when PSSS level corresponded to 2 or 3, while heart rate, oxygen saturation, and cerebral rSO_2 were stable.

Figure 8a, 8b, 8c: setting in our department in which sedoanalgesia was performed

7. DATA COLLECTION

Most of the data (HR, SpO_2, $EtCO_2$ and NIRS) were recorded every 2 minutes from the moment the sensors were applied on the patient's forehead to the emergence from anesthesia. Differently, if at all possible, PSI values and PSSS were recorded every minute. Pharmacological agents and their dosages were recorded at the exact

time of their administration. Along with the procedure, the operator also recorded when the noxious stimulus was applied (e.g. puncture of the skin, lumbar puncture, bone aspirate) and if the patient reacted to the stimulus (+) or not (-). A response to the stimulus was considered *positive* if the patient moved, manifested pain vocally or through facial expressions. A response to the stimulus was considered *negative* if the patient did not manifest pain or movements.

8. DATA ANALYSIS

NIRS, PSI and PSSS were evaluated on their ability to provide different information during the sedoanalgesia procedure and if these information result to be useful in order to conduct an efficient sedation.

- To understand the fluctuations of NIRS, PSI and PSSS values in relation to drug administration, we compared the three scales at t_0 and t_2, i.e. in the initial phase of sedation. The administration of the drug always occurred within these two minutes (see definition of "*Starting point of sedation, t_0*"). Furthermore, we evaluated the safety of sedation during the procedure, recording all values of NIRS under 60%, PSI under 30 and PSSS above 3 or under 2, which are considered potentially at risk during sedation. Furthermore, the total amount of adverse reactions was noted.
- We evaluated possible distinct effects of different sedation drugs, and their impact on each scale (see paragraph 8.1 "*Subgroups of population*")
- Onset of adverse reactions was studied considering their seriousness and their possible interference with continuing the procedure. We also checked for possible correlation between adverse effects and anomalous values of NIRS or PSI, or with excessive and sudden drop in the patient state of consciousness (PSSS).
- Finally, some considerations about noxious stimuli were made. Specifically, we checked if positive or negative response to painful stimuli was dependent on the patients' state of consciousness as well as on their PSI level. In order to achieve this goal, we used a PSI cut off of <70, under which "deep sedation" starts, and we correlated positive or negative response to stimuli with values above or under 70. We also analyzed if painful stimuli provoked

a change in the patient's behavior and, consequently, on the PSSS, comparing PSSS values before and after painful stimuli.

8.1 Population subgroups

In order to highlight possible differences and affinities between the three scales, we planned to subdivide the whole population into three groups: one receiving ketamine and propofol (KET+PPF), one receiving fentanyl and propofol (FNT+PPF), and one receiving ketamine only (KET). As we expected the majority of patients to be treated with KET+PPF and FNT+PPF, comparisons between these two subgroups were made. All other patients were considered in overall data.

The impact of different drugs on NIRS was analyzed by examining their relationship with prevalence of pathological (<60%) and borderline (60-70%) NIRS levels, respectively.

Similarly, different drugs were also evaluated by comparing PSI changes before and after each single bolus of PPF, KET and FNT, both in absolute and percentage values, considering a delta greater than 5% as notable.

Furthermore, we evaluated which combination of drugs was able to maintain PSI values within the safe rage (30-70) by analyzing each sedation's PSI values and classifying each result into three subgroups (<30, 30-70, >70). We also verified if any combination of drugs was more correlated with pathological PSI values (<30).

Besides, we investigated which combination of drugs was more likely to be associated to PSSS values of 2 and 3, clinically corresponding to a safe and efficient sedation, throughout at least 90% of the procedure.

Finally, we evaluated if different combination of drugs were more likely to be associated with adverse reactions, as well as negative response to noxious stimuli.

Descriptive statistics will be reported as median and range, mean and standard deviation, interquartile range (IQR) for continuous variables, and as a proportion and percentage for categorical variables. T student test, Wilcoxon test, chi-square 2x2 will be performed in order to highlight possible confrontations.

Data will be transcript and analyzed in Excel sheets, while statistical calculation will be performed with a statistical software (JAMOVI 2.3.38, May 2023).

RESULTS

1. STUDY POPULATION

1.1 General population

Thirty-five patients were included in our study and underwent 77 sedo-analgesia sessions. Nineteen patients underwent one session (54.3%), 16 patients required repeated sessions (45.7%), up to a maximum of 9 sessions per child (median 1, range 1-9). Overall, 90 painful or invasive procedures were performed. Twelve sessions included multiple procedures (13.3%), with a maximum of 2 procedures per session.

In the group of 35 enrolled patients, median age was 6 years (range 1y 8m – 18y 8m), 13 patients were males (37,2%) and 22 (62,8%) females. Most of them were classified as ASA physical status III (80%). (*see table III for a detailed descriptive analysis)*

Table III. Descriptive analysis of 35 patients, considering actual age and weight at the time of the session

Median age	6y (range 1y 8m - 18y 8m)
Sex	M 13 (37,2%) F (62,8%)
Median weight	22kg (range 13-64 kg)
Diagnosis	
Oncoematologic disease	29 (82,8%)
Cystic Fibrosis	2 (5,7%)
Encephalitis	1 (2,8%)
Osteomyelitis	1 (2,8%)
Plastic Surgery	1 (2,8%)
Neuromyelitis optica	1 (2,8%)

Out of 90 procedures, 46 were therapeutic or diagnostic lumbar punctures (51,1%), 36 bone aspirates (40%), 2 bone biopsy (2,2%), 2 vascular peripheral access positioning (2,2%), one central venous catheter positioning (1,1%), one electromyography (1,1%), two wound medication (2,2). The more common procedure association was lumbar puncture with bone aspirate (15 cases out of 77 sedations, 19,5%).

The median length of all sessions was 16 minutes (range 4min-70min), with a mean duration of 18,5 minutes.

The most used drug was intravenous propofol, used in 70 procedures (91%), but never mono-therapeutically. In addition to propofol, ketamine was used during 36 procedures (46,8%) and fentanyl during 34 procedures (44,2%). In 7 cases ketamine was used alone (9,1%). Six children needed a pre-medication with midazolam (7,8%) *(See table IV for session characteristics analysis).*

Table IV. clinical characteristics of 77 sessions. CVP: peripheral venous catheter, CVC: central venous catheter

Procedures performed per session	**Total sessions=77**
Lumbar Puncture	35 (45,5%)
Bone aspirate	19 (24,7%)
Lumbar puncture+Bone aspirate	15 (19,5%)
Bone aspirate+Bone biopsy	2 (2,2%)
CVP positioning	2 (2,2%)
Electromyography	1 (1,1%)
CVC positioning	1 (1,1%)
Wound medication	2 (2,2%)
Median session duration (min)	16 minutes (range 4-70)
Drugs administered	
Ketamine+Propofol	36 (46,8%)
Fentanyl+Propofol	34 (44,2%)
Ketamine	7 (9%)

1.1 Study population subgroups

Table V: Population subgroups according to different administered drugs used during the sessions. CVP: peripheral venous catheter, CVC: central venous catheter

	Ketamine+Propofol (36 sessions)	**Fentanyl+Propofol (34 sessions)**	**Ketamine (7 sessions)**
Number of patients	19	23	7
Sex	M 7 (36,8%) F 12 (63,2%)	M 10 (43,4%) F 13 (56,6%)	M 2 (28,6%) F 5 (71,4%)
Median age (range)	4 y (1y –18y)	6 y 6 m (2y – 18y)	4 y (6y – 10m)

Median weight (range)	16kg (10kg – 46kg)	27kg (12kg – 64kg)	17 kg (10kg – 26kg)
Underlying Pathology	Oncology patients: 17 (89,7%) Osteomielitis: 1 (5,3%) Plastic Surgery patient: 1 (5,3%)	Oncology patients: 21 (91,3%) Cystic Fibrosis: 1 (4,3%) Neuromyelitis optica: 1 (4,3%)	Oncology patients: 3 (42,8%) Cystic Fibrosis:1 (14,3%) Plastic Surgery patient: 1 (14,3%) Kawasaki's Disease: 1 (14,3%) Encephalitis: 1 (14,3%)
Type of procedure	Bone aspirate: 7 (19,4%) Bone aspirate + Bone biopsy: 1 (2,7%) Bone aspirate + Lumbar Puncture: 9 (25%) Lumbar Puncture: 16 (44,4%) Electromyography: 1 (2,7%) Positioning of CVC: 1 (2,7%) Wound medication: 1 (2,7%)	Bone aspirate: 12 (35,2%) Bone aspirate + Bone biopsy: 1 (2,9%) Bone aspirate + Lumbar Puncture: 6 (17,6%) Lumbar Puncture: 15 (44,1%)	Lumbar Puncture: 4 (57%) Positioning of CVP: 2 (29%) Wound medication: 1 (14%)

Subgroups treated with the combination of KET+PPF and FNT+PPF were comparable, in terms of type of procedures performed, median session length and number of sessions. As for demographic features, median age and weight of the KET+PPF subgroup were lower than FNT+PPF (p. 0.05).

2. INITIAL DATA

The starting NIRS value was recorded in 48/77 sessions (62.3%), while the starting PSI median value was measured in 61 sessions (79,2%). In the remaining 15 and 16 sessions respectively, it was not possible to measure the NIRS or PSI either due

to technical problems or because the patient's agitation did not allow the electrodes to be positioned before the start of sedation.

About PSSS, out of 77 sessions, 57 sedations were adequate (74%), 2 session (2,6%) showed over-sedation (PSSS of 0 or 1), and 16 (20,8%) showed under-sedation (PSSS of 4 or 5). In two cases the PSSS was not recorded.

3. VARIATION OF NIRS, PSI AND PSSS VALUES

To compare the three scales, we evaluated NIRS, PSI and PSSS values in t_0 and t_2, respectively, according to different combinations of drugs.

Table VI: descriptive statistical analysis of right (r-NIRS) and left (l-NIRS) NIRS values during the sessions by using KET+PPF and FNT+PPF. N: number of sessions, SD: standard deviation, IQR: interquartile range, Min: minimum value, Max: maximum value, perc.: percentile.

	KET+PPF (36 sessions)				**FNT+PPF (34 sessions)**			
	r-NIRS		l-NIRS		r-NIRS		l-NIRS	
	T_0	T_2	T_0	T_2	T_0	T_2	T_0	T_2
N	16	20	16	20	23	28	22	28
Missing	20	16	20	16	11	6	12	6
Mean	76,1	77	79,2	79,2	78,6	78,4	77,7	78,7
Median	76,5	77	80	80	79	77,5	78	79,5
SD	4,5	5,4	5,5	5,5	7,1	6,4	5,8	6
IQR	4	7,2	5	5,5	8,5	8	8	8
Min	63	66	69	69	64	67	68	68
Max	83	86	89	95	98	98	88	89
25th perc.	74	74	76,7	75,7	74	74	73	75
50th perc.	76,5	77	80	80	79	77,5	78	79,5
75th perc.	78	81,2	81,7	81,2	82,5	82	81	83

Table VII: descriptive statistical analysis of PSI values during the sessions by using KET+PPF and FNT+PPF. N: number of sessions, SD: standard deviation, IQR: interquartile range, Min: minimum value, Max: maximum value, perc.: percentile.

	KET+PPF		**FNT+PPF**	
	PSI		PSI	
	T_0	T_2	T_0	T_2
N	28	30	28	32
Missing	8	6	6	2

Mean	96,6	**70,5**	92,1	**62**
Median	100	**74**	94	**60,5**
SD	4,5	18,3	11,4	18,2
IQR	7,2	17,2	9	27,7
Min	73	22	45	30
Max	100	92	100	88
25th perc.	92,7	67,2	91	49
50th perc.	100	74	94	60,5
75th perc.	100	84,5	100	76,7

* p<0,001; **p<0,001

Table VIII: descriptive statistical analysis of PSSS values during the sessions by using KET+PPF and FNT+PPF. N: number of sessions, SD: standard deviation, IQR: interquartile range, Min: minimum value, Max: maximum value, perc.: percentile.

	KET+PPF		**FNT+PPF**	
	PSSS		PSSS	
	T_0	T_2	T_0	T_2
N	35	35	33	34
Missing	1	1	1	0
Mean	3,6	2,3	3,3	2,2
Median	3	**2***	3	2*
SD	0,7	0,5	0,6	0,6
IQR	2	0	1	0
Min	2	2	2	1
Max	5	4	5	4
25th perc.	2	2	2	2
50th perc.	3	2	2	2
75th perc.	4	2	3	2

*p=0,001

Table IX*:* statistical analysis

		Test	**p**
PSI t_0 KET+PPF	**PSI t_2 KET+PPF**	t di Student	<0,001
PSI t_0 FNT+PPF	**PSI t_2 FNT+PPF**	t di Student	<0,001
PSI t_2 FNT+PPF	**PSI t_2 KET+PPF**	W di Wilcoxon	0,7
PSSS t_0 FNT+PPF	**PSSS t_2 FNT+PPF**	t di Student	<0,001

PSSS t_0 KET+PPF	**PSSS t_2 KET+PPF**	t di Student	<0,001
PSSS t_2 KET+PPF	**PSSS t_2 FNT+PPF**	W di Wilcoxon	0,3

1. SAFETY AND EFFICACY OF SEDO-ANALGESIA

None of NIRS registered values was <60% during all sessions. Overall, 971 values of PSI were recorded. Nineteen values out of 971 (1,95%) were <30.

Twelve sessions out of 77 performed (15%) had the onset of adverse reactions (see paragraph 6 *"Adverse events"* for a more detailed descriptive analysis).

2. EFFECT OF DIFFERENT DRUGS, SINGLE OR IN COMBINATION, TO NIRS, PSI AND PSSS VALUES.

2.1 NIRS

Thirty-six sessions (45,7%) were conducted with KET+PPF. In 15 cases (41,7%) it was not possible to detect NIRS values. In the other 21 sessions (58,3%), we recorded 233 values for the right hemisphere and 233 values for the left hemisphere.

Thirty-four sessions (44,1%) were conducted with FNT+PPF. In 3 cases (8,8%) it was not possible to detect NIRS values. In the other 31 patients (91,1%), we detected 242 values for the right hemisphere and 249 values for the left hemisphere (see *table X* for detailed NIRS values).

We did not observe significant variations in NIRS values during the procedure.

Table X: Detailed characteristics of recorded NIRS data. r-NIRS: right NIRS, l-NIRS: left NIRS

	r- NIRS	**l- NIRS**
KET+PPF	Total: 233 values >70%: 205 values 60-70%: 28 values	Total: 233 values >70%: 225 values 60-70%: 8 values
FNT+PPF	Total: 242 values >70%: 235 values 60-70%: 7 values	Total: 249 values >70%: 233 values 60-70%: 16 values

2.2 PSI

Administration of a single bolus of PPF significantly reduced PSI >5% in 66.7% of cases. Instead, KET and FNT did not influence PSI.

Overall, the combination of FNT+PPF was more frequently associated to PSI values between 30 and 70, as well as to lower PSI values (<70) compared to KET+PPF (p=<0.001, p=<0.001).

Table XI: distribution of PSI values during the sessions by using KET+PPF and FNT+PPF

	>70	**30-70**	**<30**
KET+PPF	388	195	9
FNT+PPF	181	243	13

2.3 CLINICAL EVALUATION

2.3.1 PSSS

In clinical terms, both FNT+PPF and KET+PPF sedation were adequate in 65.7% and 82.4% of cases, respectively (p. NS). Moreover, PSI between 30 and 70 is associated with a clinically adequate sedation.

Table XII*:* clinical evaluation of sedation by using KET+PPF and FNT+PPF

Clinically adequate sedation	**Clinically inadequate sedation**
KET+PPF: 28/34 (82,4%) FNT+PPF: 23/35 (65,7%)	KET+PPF: 6/34 (17,6%) FNT+PPF: 12/35 (34,3%)

Table XIII*:* clinical evaluation of sedation when PSI is between 30 and 70

	PSSS 0-1	**PSSS 2-3**	**PSSS 4**
PSI 30-70	4	425	13

2.3.2 Noxious stimuli

Overall, 201 painful stimuli were performed in 77 sessions. Patients reacted positively to the stimulus in 74 cases (27,2%), while they did not respond in 127 (63,2%).

NIRS and PSSS values did not significantly change in correspondence of the stimulus and 2 minutes later. PSI values were available for 185 stimuli, as 16 cases were missing. A negative response to noxious stimuli was significantly associated with a PSI value <70. (p=0.001).

Table XIII: distribution of PSI values when a positive or negative response to stimuli was obtained.

Positive response to stimulus	**Negative response to stimulus**
PSI>70: 46/91 (50,5%) PSI<70: 23/94(24,5%)	PSI>70: 45/91 (49,5%) PSI<70: 71/94 (75,5%)

***Table XIV*:** distribution of positive or negative response to stimuli by using KET+PPF and FNT+PPF

Positive response to stimulus	**Negative response to stimulus**
KET+PPF: 39/115 (33,9%) FNT+PPF: 26/71 (36,6%)	KET+PPF: 76/115 (66%) FNT+PPF: 45/71 (63,4%)

Considering only population treated with the combination FNT+PPF or KET+PPF, administered stimuli were 186. One hundred and fifteen were administered to patients treated with KET+PPF (61,8%), while 71 were administered to patients treated with FNT+PPF (38,2%). Overall, the administration of KET+PPF or FNT+PPF was not associated with a positive stimulus response (p=0,7).

1. ADVERSE EVENTS

We observed adverse events in 12 sessions out of 77 (15,6%). In seven sessions mild desaturation (SpO2 >85%) were registered, but the session could be continued and completed by positioning of a O_2 mask. In other 2 episodes an apnea occurred but we didn't have to interrupt the session. In one case the patient manifested retching, but after a short pause the session could be successfully completed.

Another child presented itchy face, and we had to remove electrodes. One procedure was interrupted due to the need to ventilate the patient (1.2%).

Out of 12 adverse events, 9 cases were associated with the administration of FNT+PPF (75%) and 3 cases with administration of KET+PPF (25%) (p 0.04).

FNT+ PPF	**R-NIRS**	**L-NIRS**	**PSI**	**PSSS**
Mild desaturation SpO2>85%	88	92	19	1
Apnea	82	85	55	1
Mild desaturation SpO2>85%	71	76	88	1
Itchy face	75	72	nr	4
Mild desaturation SpO2>85%	82	80	37	1
Mild desaturation SpO2>85%	86	82	49	1
Mild desaturation SpO2>85%	nr	nr	52	1
Apnea	85	85	50	0
Retching	79	94	50	3
KET+PPF	**R-NIRS**	**L-NIRS**	**PSI**	**PSSS**
Mild desaturation SpO2>85%	83	88	19	1
Apnea	nr	nr	nr	1
Mild desaturation SpO2>85%	73	72	59	1

DISCUSSION

In this study, we examined different measures to detect cerebral activity in pediatric patients during sedoanalgesia: PSSS through the clinical evaluation of child's behavior, PSI through SedLine, and cerebral rSO2 through NIRS technology.

Clinical scales such as the PSSS are commonly used to assess pain perception during painful procedures[10,27]. Recently, Lorenc et al. used the PSSS to assess the degree of discomfort of the pediatric patient during peripheral intravenous insertion and specimen collection. This study demonstrated that the use of sedative, anxiolytic, and analgesic medications improved procedural comfort scores from 68% to 90% of pediatric patients[30]. Our study confirms that the administration of sedative analgesia improves patient comfort, significantly reducing PSSS after drugs administration. Comparing drug combinations, PSSS evaluation showed that both PPF+FNT and PPF+KET combinations ensure a significant reduction in PSSS and non-perception of painful stimulus. However, several studies showing that the KET+PPF combination provides better and more comfortable sedoanalgesia, due to lower propofol consumption, more stable blood pressure and heart rate, better peripheral oxygen saturation and faster recovery time[31-33].

Our study showed that a PSSS value of 2-3 was associated with PSI between 30 and 70 in 96.15% of cases. In addition, observing the links between PSI values and positive responses to noxious stimuli, we found a lower response to painful stimuli when the PSI was <70.

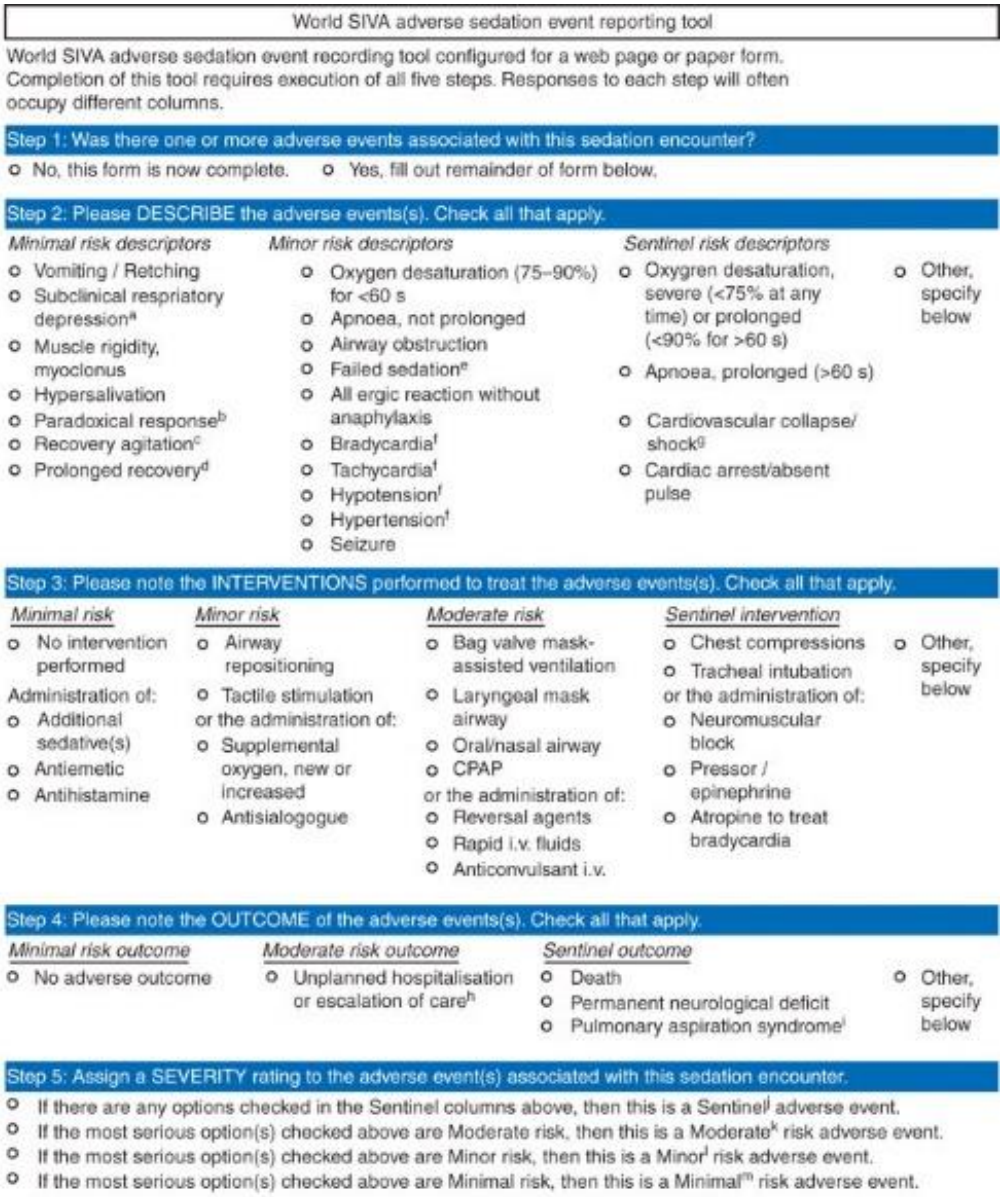
Indeed, it has been shown that PSI values >80 indicate a state of wakefulness, whereas values under 20 indicate burst suppression. The correct general anesthesia depth indicated by the manufacturer implies a PSI value between 25 and 50[26]. To our knowledge, the optimal PSI level for conscious sedation in spontaneous breathing patients has not been investigated yet. Our study showed that maintaining PSI between 30 and 70 may result in effective and safe sedation. However, since very few studies have been conducted in children or adults receiving sedation during PSI monitoring, a larger cohort of patients are needed to confirm these findings.

We have also considered changes from baseline in PSI values one minute after PPF, KET or FNT administration. Our results showed that PPF significantly reduced the patients' state of consciousness and consequently the PSI values. This finding agrees with the pharmacological effect of propofol that is a sedative-hypnotic anesthetic. Previously, Lee et al investigated the ability of PSI to reflect the level of sedation during target-controlled propofol infusion comparing PSI values to Modified Observer's Assessment of Alertness/Sedation (MOAA/S), a validated 6-point scale assessing responsiveness of patients during sedation. In their study, they found significant correlation between PSI values and MOAA/S scales, demonstrating that PSI values corresponded to the various depths of sedation during PPF infusion[34]. On the other hand, we did not find any consistent change in PSI values after fentanyl or ketamine administration. Currently, no human studies have been conducted to investigate the correlation between intravenous ketamine and/or fentanyl and PSI changes.

Finally, about cerebral rSO2, we did not find significant variations in NIRS during the procedure. Typically, we expected that painful stimuli would have caused an increase in blood flow to the brain, altering NIRS values. Instead, we did not observe any significant change, neither in r-NIRS nor in l-NIRS. Two other studies have shown that changes in NIRS are sudden and occur within the first 10-60 seconds[35,36]. Thus, we did not detect changes maybe because data were collected every 120 seconds. Therefore, to highlight alterations in cerebral oxygenation after a painful stimulus, data should have been registered more frequently (e.g., every 10 seconds), but this was not among the objectives of our study.

In terms of safety, out of 77 sessions we observed 12 adverse reactions, of which only one was severe.

The spectrum of seriousness of adverse events during procedural sedation is wide. A serious adverse event (SAE) may include apnea, hypotension, laryngospasm, bradycardia, clinically apparent pulmonary aspiration, complete airway obstruction, and permanent neurological damage or even death. The interventions and the promptness performed in response to SAE such as positive pressure ventilation, administration of vasoactive or neuromuscular blockade drugs, and endotracheal intubation or chest compressions are considered significant[37].



World SIVA adverse sedation event reporting tool

World SIVA adverse sedation event recording tool configured for a web page or paper form. Completion of this tool requires execution of all five steps. Responses to each step will often occupy different columns.

Step 1: Was there one or more adverse events associated with this sedation encounter?

- o No, this form is now complete.
- o Yes, fill out remainder of form below.

Step 2: Please DESCRIBE the adverse events(s). Check all that apply.

Minimal risk descriptors
- o Vomiting / Retching
- o Subclinical respriatory depression[a]
- o Muscle rigidity, myoclonus
- o Hypersalivation
- o Paradoxical response[b]
- o Recovery agitation[c]
- o Prolonged recovery[d]

Minor risk descriptors
- o Oxygen desaturation (75–90%) for <60 s
- o Apnoea, not prolonged
- o Airway obstruction
- o Failed sedation[e]
- o All ergic reaction without anaphylaxis
- o Bradycardia[f]
- o Tachycardia[f]
- o Hypotension[f]
- o Hypertension[f]
- o Seizure

Sentinel risk descriptors
- o Oxygren desaturation, severe (<75% at any time) or prolonged (<90% for >60 s)
- o Apnoea, prolonged (>60 s)
- o Cardiovascular collapse/ shock[g]
- o Cardiac arrest/absent pulse

- o Other, specify below

Step 3: Please note the INTERVENTIONS performed to treat the adverse events(s). Check all that apply.

Minimal risk
- o No intervention performed

Administration of:
- o Additional sedative(s)
- o Antiemetic
- o Antihistamine

Minor risk
- o Airway repositioning
- o Tactile stimulation

or the administration of:
- o Supplemental oxygen, new or increased
- o Antisialogogue

Moderate risk
- o Bag valve mask-assisted ventilation
- o Laryngeal mask airway
- o Oral/nasal airway
- o CPAP

or the administration of:
- o Reversal agents
- o Rapid i.v. fluids
- o Anticonvulsant i.v.

Sentinel intervention
- o Chest compressions
- o Tracheal intubation

or the administration of:
- o Neuromuscular block
- o Pressor / epinephrine
- o Atropine to treat bradycardia

- o Other, specify below

Step 4: Please note the OUTCOME of the adverse events(s). Check all that apply.

Minimal risk outcome
- o No adverse outcome

Moderate risk outcome
- o Unplanned hospitalisation or escalation of care[h]

Sentinel outcome
- o Death
- o Permanent neurological deficit
- o Pulmonary aspiration syndrome[i]

- o Other, specify below

Step 5: Assign a SEVERITY rating to the adverse event(s) associated with this sedation encounter.

- o If there are any options checked in the Sentinel columns above, then this is a Sentinel[j] adverse event.
- o If the most serious option(s) checked above are Moderate risk, then this is a Moderate[k] risk adverse event.
- o If the most serious option(s) checked above are Minor risk, then this is a Minor[l] risk adverse event.
- o If the most serious option(s) checked above are Minimal risk, then this is a Minimal[m] risk adverse event.

Figure 2: World SIVA adverse sedation event reporting tool: variables and outcomes[28]

Recently Bhatt *et al* studied adverse reactions in the emergency department, highlighting that the most frequent adverse reactions were oxygen desaturation and vomiting[38]. The low rate of severe adverse events supports the safety of procedural sedation when performed by emergency department physicians[38]. Our results are in line with those reported by Bhatt et al.; in fact, only in one case we had to interrupt the procedure and ventilate the patient.

Even though the relatively low incidence of adverse reactions precludes firm deductions, it is interesting to note that most adverse events were registered in children treated with the combination of PPF+FNT. As mentioned before, the combination of KET+PPF has surely proven to be safer, even if adverse reactions are concerned[31-33]. The combination of different types of drugs needs to be individualized based upon patient and procedure characteristics. For example, compared with midazolam-opioids for procedural sedation and analgesia in the acute care setting, ketamine has shown to be associated with fewer respiratory adverse events, sedation recovery time is shortest with propofol, and patient satisfaction is highest using a combination of ketamine-propofol. Compared with ketamine-propofol, propofol-opioids may be associated with higher rates of respiratory and cardiac adverse events, and probably fewer gastrointestinal adverse events[39].

No alterations in NIRS, PSI or PSSS has been highlighted during the onset of adverse stimuli. This finding may be explained considering that adverse reactions may be related to the administration of PPF more than to incorrect sedation. Moreover, it was interesting that NIRS values were not influenced by desaturation episodes. Since lowering values indicate lack of oxygenation or an increased metabolic rate on the tissue examined, we can speculate that sedations did not cause cerebral deoxygenation in our patients and could be considered safe.

STUDY LIMITATION

Our study has several limitations. First, our sample size was relatively small, limiting our ability to draw firm conclusions. Second, the recruited population was not uniform regarding the type of intervention performed during the study. In fact, different procedures could have been associated with distinct pain intensity according to the type of stimulus administered.

Third, despite our planned study design, some data regarding NIRS and PSI were not available, due to device malfunctioning or to the fact that optodes and electrodes sometimes made the child uncomfortable. Indeed, in order to avoid increasing anxiousness in the patients, at times it was necessary to place the sensors when the child was already asleep and remove them before the child woke up, thus resulting in some missing data.

Finally, the fact that the monitoring values were visible during the procedure may have led physicians to adapt the sedation technique differently than they would have done without seeing the screen.

CONCLUSIONS AND FUTURE PERSPECTIVES

Safety and efficacy of sedation, along with pain control, are very important issues during diagnostic and therapeutic invasive procedures in hospitalized children. As children may need to undergo multiple procedures, the medical staff should avoid the onset of negative memory and post-traumatic stress as much as feasible.

Despite the growing interest on pain management in children, to date adequate monitoring of sedation is not routinely made, while clinicians entrust international guidelines and their experience based on the child's characteristics. Despite different scales and methods of monitoring sedation have been developed, to our knowledge none of them have been studied when concomitantly applied to sedated pediatric patients.

In our study, we observed that all the scales may give specific information from different points of view. PSSS is a behavioral scale which, in our study, gave information about safety and adequacy of sedation. PSI has proven to be the most fluctuating scale, reflecting patient's state of consciousness and being modified by the administration of drugs and the application of noxious stimuli. It was interesting to notice that patients' negative response to pain strongly correlated with PSI value<70. NIRS technology reflects brain oxygenation, and in our study testified that no dangerous cerebral desaturation happened.

Of the three scales, PSSS was most used clinically by clinicians, as when the child exhibited intentional movements or pain, sedation was adjusted regardless of PSI or NIRS values.

Despite our study suggests a potential useful role of brain monitoring during sedoanalgesia in children, further research performed in larger and more homogenous samples is needed to confirm our preliminary observations.

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