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STUDY PROTOCOL

"NOL Index and Sedation: no pain or no memory?"

Acronym: SedNOL

v. 1.0 dated 23/10/2023

Sponsor:
Azienda Sanitaria Locale of Novara- "Ss. Trinità of Borgomanero" Hospital

Principal Investigator:
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Study Type:
Prospective, single-center, observational cohort study, non-pharmacological, non-profit

Participating Centers:
Department of Anesthesia and Intensive Care Unit in "Ss. Trinità of Borgomanero" Hospital

Sponsor:
None

Version Date 1.0:
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Confidential

Introduction and Background

The term "nociception" refers to the neural process of encoding noxious stimuli (Loeser, 2008), processed by the peripheral and central nervous system (PNS/CNS) (Institute of Medicine, 1987) upon activation of nociceptors. Thus, noxious stimuli, including tissue damage, activate nociceptors in peripheral structures and transmit information to the dorsal horn of the spinal cord, then through ascending spinal pathways to the thalamus and cortical and subcortical structures that process this information, generating various types of responses: motor, emotional, memory, etc. The term pain is reserved for the conscious perception of actual or potential tissue damage and therefore cannot be used in an unconscious state.

General anesthesia is a state of pharmacologically induced, temporary, and reversible coma consisting of three elements: hypnosis, analgesia, and muscle relaxation. These are achieved by administering two or more drugs to the patient, inducing an artificial sleep so deep that it allows any surgical procedure to be performed without feeling any pain, moving, or remembering anything. This means that any noxious stimulus is neither processed nor recognized by the brain while anesthesia is in progress. This technique is typically used for long-duration or very painful procedures (ISSalute, 2022).

Deep sedation is defined as a drug-induced depression of consciousness during which patients cannot be easily awakened but respond to repeated or painful stimulation. In this state, the ability to maintain independent ventilatory function may be compromised, often requiring assistance to maintain airway patency. Spontaneous ventilation may be inadequate, whereas cardiovascular function is usually maintained (2019). Sedation is a continuum and can progress or regress from one level to another, inevitably varying the risks and appropriate management to preserve patient safety. Monitoring vital parameters, always combined with careful clinical assessment, is therefore indispensable and adjustable as needed (SIAARTI-SIED, 2022).

Deep sedation may be the anesthetic technique of choice for short-duration, particularly painful day-surgery procedures where complete patient curarization is not strictly necessary. Various drugs in current clinical practice can ensure an adequate sedation plan for the procedure, which can be used alone or in combination and administered as a single dose or continuous infusion.

In addition to standard perioperative monitoring, monitoring the depth of anesthesia is highly recommended by international scientific literature, especially in cases where a protocol involving Propofol infusion in TIVA-TCI (Total IntraVenous Anesthesia - Target Controlled Infusion) is used (Klein AA, 2021). Conversely, there is currently no recommendation or guideline for nociception monitoring. Nociception is typically assessed using indirect methods such as heart rate and blood pressure variations. However, these indicators have been shown to be poor surrogates for nociception monitoring, as vital signs are influenced by a range of other health conditions (Coluzzi, 2019).

Various other methods have been used to establish the efficacy of analgesics during the intraoperative period, such as evaluating patient movement and sweating. However, these indirect parameters are largely imprecise because different anesthetic drugs reduce and/or abolish the autonomic nervous system's ability to respond to nociceptive stimuli to varying degrees (Kang, 2015). Nevertheless, maintaining the balance between nociception and analgesia (the "nociception-antinociception balance") is critical to avoid serious postoperative complications (Ghanty, 2019).

It should also be noted that the lack of accurate nociception monitoring during surgery can lead to inadequate analgesic doses. Opioid analgesics are widely used in common clinical anesthetic practice, and administering an insufficient dose could lead to abnormal recovery, delayed hospital discharge, and, in some cases, chronic postoperative pain. On the other hand, administering an excessive dose of opioids can cause nausea, vomiting, respiratory depression, increased hospital stay, and treatment costs (Won, 2016).

Recognizing the complexity of this process, a medical monitoring device has been developed: the PMD-200™ provides the nociception level index (NOL), an innovative technology developed by Medasense Biometrics Ltd. that allows objective measurement of patient nociception by analyzing multiple patient parameters. This device uses a non-invasive finger probe with four sensors (photoplethysmography amplitude, galvanic skin response, peripheral temperature, and accelerometry) that extract multiple pain-related physiological signals. Real-time data are analyzed by specific algorithms that identify the patient's pain pattern, displayed on a numerical scale from 0 to 100. Notably, a value of 25 indicates the threshold beyond which the nociceptive reaction is clinically significant.

The use of this tool has been extensively studied during general anesthesia, demonstrating that monitoring nociception response levels with the NOL Index can help reduce postoperative pain, patient stress hormone levels (ACTH and cortisol) (Meijer, 2020), and intraoperative opioid use, resulting in fewer hypotensive events and associated myocardial and renal damage (Meijer, 2019). Additionally, it has been shown that the combined use of the NOL Index and Bispectral Index during general anesthesia can provide accurate and complementary information to guide optimal administration of analgesic and hypnotic drugs (Meijer, 2020).

The rationale for this study lies in the context of relatively short surgical procedures (lasting between 30 and 90 minutes) requiring deep sedation anesthesia. The hypnotic efficacy of commonly used sedation protocols is widely studied and validated by international scientific literature. It is also important to consider that, in some cases, excessive administration of sedatives with insufficient analgesic coverage may occur, leading to seemingly acceptable postoperative results, while in reality, patients experience painful situations without remembering them. This can be particularly dangerous in fragile patients, where heightened adrenergic system activation leads to serious complications.

Therefore, we ask: “Are our sedation protocols, aside from their hypnotic effectiveness, equally effective at the analgesic level?”

Finally, an ethical question must also be highlighted, as proper pain management, in all its forms, is a duty the clinician must address.

Study Purpose

Evaluate the efficacy of the sedation protocol from a nociceptive perspective through continuous intraoperative nociception monitoring (NOL Index).

Primary Objective

The sedation protocol will be considered nociceptively ineffective if the percentage of time the NOL index exceeds the threshold of 25, relative to the observation time, is greater than 25%.
The NOL Index observation time is defined as the interval between reaching an adequate sedation level (Bispectral Index - BIS between 40 and 60) and the end of surgical stimulation.

Secondary Objectives

1. Time the NOL index exceeds the threshold of 25, expressed in minutes
2. Number of peaks with NOL index above 40
3. Evaluate any correlation between the primary objective and the NRS scale 15 minutes post-operation
4. Evaluate any correlation between the primary objective and the NRS scale 2 hours post-operation
5. Evaluate any correlation between the primary objective and the need for rescue analgesic doses

requested by the patient.

Study Design

Prospective observational clinical study, non-profit, non-pharmacological, utilizing the medical device PMD-200™ (Medasense Biometrics Ltd), in patients undergoing short-duration (less than 90 minutes) and particularly painful surgical procedures, with an indication for deep sedation anesthesia.

Materials and Methods

Eligibility Criteria

Inclusion Criteria

- ✓ Adult patients (>18 years old)
- ✓ ASA Physical Status I – II - III

Exclusion Criteria

- × ASA Physical Status IV
- × Pregnant or lactating patients
- × Pre-existing cardiac arrhythmias
- × Patients with neuromuscular diseases
- × Patients with psychiatric syndromes under pharmacological treatment
- × Patients with chronic continuous use of analgesics
- × Patients with a history of drug abuse
- × Allergy to one or more active ingredients used in the protocol
- × Refusal of consent

Study Population

The study population consists of patients admitted to the "Ss. Trinità of Borgomanero" hospital between March 1, 2024, and August 31, 2024, who need to undergo surgical procedures lasting less than 90 minutes and particularly painful, with an indication for deep sedation anesthesia.

Study Flow-chart

Before enrollment, upon arrival in the operating room and after being properly positioned on the operating table, patients will undergo standard intraoperative monitoring with pulse oximetry (SpO2), 3-channel electrocardiography (ECG), non-invasive blood pressure (NIBP), Bispectral Index (BIS) sensor, and a nociception sensor (NOL) will also be placed. Patients will be preoxygenated with a facial mask with FiO2 at 100% for 3 minutes. The induction phase of deep sedation anesthesia will be conducted with a single bolus of Fentanyl 1mcg/kg and TIVA-TCI of Propofol with a target-controlled infusion (Cε) concentration of 4.0 mcg/mL. As soon as the sedation plan shows a Bispectral Index between 40 and 60, the observation of the NOL Index will begin. Subsequently, the laryngeal mask will be positioned, mechanical ventilation initiated, and the surgical procedure commenced. During this phase, maintenance of the anesthesia plan will be ensured by the infusion of Propofol in TIVA-TCI with a Cε to maintain the BIS between 40 and 60, and the administration of Paracetamol 1 g, Ketorolac 30 mg, Dexamethasone 4 mg. At the end of the surgical procedure, the observation of the NOL Index will be concluded. Upon awakening, patients will be transferred to the Post-Anesthesia Care Unit (PACU), where they will remain until stabilization of vital signs. At this point, 15 minutes post-operation, the pain intensity will be recorded using the NRS scale. Subsequently, patients will be discharged to the ward,

where, at 2 hours post-operation, they will be interviewed regarding the intensity of post-operative pain and if they require any rescue analgesic doses.

Any procedures not explicitly expressed in the protocol will be performed according to normal clinical practice.

Collection and Management of Clinical Data

Data collection and management are entrusted to the investigator and/or study staff. Data collection will be directly performed on a digital file (spreadsheets - Ms. Excel - Microsoft, Redmond, CA) without the use of paper forms. Data will be collected anonymously without identifying codes that allow tracing back to the patient's folder and therefore to the patient's identity. The correspondence list between demographic data and patient identification codes will be kept at the enrolling center, and only the study staff will have access to it. The collected data will include the following:

Anthropometric Data

- Gender
- Age
- Weight
- Height
- Body Mass Index - BMI
- ASA Physical Status

Clinical Data

- Surgical Procedure performed
- Heart Rate (HR)
- Non-invasive Blood Pressure (NIBP)
- Pulse Oximetry (SpO2)
- Bispectral Index (BIS)
- NOL Index
- NRS Pain Scale

Statistical Analysis

Continuous variables will be presented as mean and standard deviation or as median and interquartile range depending on the distribution. Normal distribution will be assessed using the Kolmogorov-Smirnov test. Any sub-analyses and comparisons between subgroups will be performed using Student's t-test for parametric data, while the Mann-Whitney test will be used for non-parametric data. Categorical variables will be presented as absolute number and percentage relative to the total sample size. Any sub-analyses and comparisons between subgroups will be performed using the chi-square test or Fisher's exact test depending on the subgroup sizes. In all cases, the null hypothesis will be rejected for values of $\alpha < 0.05$. The software used for data analysis and sample sizing is Medcalc v. 22.013 (MedCalc Software, Ostend, Belgium).

Sample Size Determination

Following the manufacturer's indications, a nociceptive response measured at NOL >25 is considered

positive. In the absence of similar studies and reference parameters, we have set, based on clinical experience, a mean ≤ 10% of the observation interval, with NOL ≥ 25, as not significant for the presence of a nociceptive stimulus (Null Hypothesis). We have also considered a mean ≥ 25% of the observation interval, with NOL ≥ 25, as significant for the presence of a nociceptive stimulus. By calculating the sample size for a single mean, setting the type I error α to 0.05, power β to 0.8, estimating a standard deviation of 30%, the sample size in the study is determined to be 34 subjects.

Approval from the Competent Authority

In accordance with current regulations, the principal investigator must obtain approval from the appropriate Competent Authority before commencing the clinical study. This study will be conducted in accordance with the rules of ICH/GCP (International Conference of Harmonization/Good Clinical Practice) and all applicable laws, including the Helsinki Declaration of June 1964, modified by the latest World Medical Association General Assembly, Seoul 2008. As this is a non-interventional study, there are no specific risks associated with participating in the study protocol. Participation does not entail direct benefits to the enrolled patient but will contribute to improving knowledge regarding nociceptive stimulation during deep sedation anesthesia for patients undergoing short-duration and particularly painful surgical procedures.

Ethics Committee Approval

The investigator must ensure that the protocol has been reviewed and approved by the local independent Ethics Committee before commencing the study. The Ethics Committee must also review and approve the informed consent (IC) form and all written information provided to the patient before enrollment in the study. If it is necessary to modify the protocol and/or the IC during the study, the investigator will be responsible for ensuring the review and approval of such documents as requested by the Ethics Committee. The content of such modifications will be implemented only after approval by the Ethics Committee. Until then, reference should be made to the previous version of the already approved document.

Informed Consent

The investigator or other designated personnel is responsible for informing individuals about all aspects and procedures of the study. The IC must comply with current regulatory procedures: Helsinki Declaration (WMA, 2013 latest version, §§ 25-32), Reg. (EU) 536/2014, Charter of Fundamental Rights of the European Union (Nice, 2000, art. 3). The investigator (and/or designated collaborator) and the subject being offered the study must sign the IC form before the patient initiates any procedures indicated in the study. The subject will receive a dated and signed copy of the IC from both parties, and the original copy will be kept in the designated archives for the study. The subject's decision to participate or not in the study must be entirely voluntary. The participating subject has the right to withdraw their consent at any time.

Confidentiality

The study's Responsible Party ensures that the data of the patients enrolled during the study will be safeguarded, stored, and processed in full compliance with privacy regulations, particularly Legislative Decree no. 196/2003 and subsequent amendments ("Privacy Code"), the Deontological Code regarding data processing for statistical-scientific purposes, and the "Guidelines for the processing of personal data within the scope of clinical trials of medicinal products" published in the Official Gazette no. 190 of August 14, 2008, and EU Regulation 2016/679. The Investigator and the personnel involved in the study must keep all received information (including the protocol), data obtained, and documentation generated during the study confidential and will not use the information, data, and reports for purposes other than the protocol. These restrictions do not apply to: 1) information that becomes publicly available but not due to negligence of the Investigator or their staff; 2) information that must be disclosed confidentially to the Ethics Committee or the Institution's Review Board for the sole purpose of allowing the evaluation of the study; 3) information that must be disclosed to obtain appropriate medical care for a subject in the study.

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