Study protocol

Observation of clinical effects of oxygen: nitrogen 50%:50% gas mixture application for minor invasive procedures in pediatric patients

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Summary

Rationale

Reducing pain and anxiety, avoiding psychological trauma associated with medical procedures are the focus of pediatric anesthesiologist in everyday practice. Nitrous oxide is a useful option for children who require procedural sedation. It is easy to apply, has satisfactory sedative and analgetic effects. Side effects are transient and vanish after discontinuation. It has been used for decades in pediatric emergency department as well for procedural sedation and analgesia.

Objective

The aim of this study is to evaluate the analgetic and anxiolytic profile of oxygen: nitrogen 50%:50% gas mixture for minor invasive procedures in pediatric patients.

Study design

Single center prospective observational cohort study.

Study population

Patients from 1 to 16 years of age admitted to department of anesthesiology and intensive care therapy, Institute for mother and child health care. Inclusion criteria: age 1-16 years; patients scheduled for following procedures : venepunction, arterial line placement, nasogastric tube placement, urinary catheter placement, removal of thoracic drain, skin suture. Exclusion criteria, presence one of the following conditions: age <1 year or > 16 years; pneumothorax; pneumoperitoneum; pneumocephalus; otitis media; obstructive lung disease; upper airway infection; methylenetetrahydrofolate reductase (MTHF) deficiency; vitamin B12 deficiency; megaloblastic anemia; folate deficiency (Vitamin B9 deficiency); bleomycin sulphate therapy; neuropathy, pregnancy.

Main study endpoints

Primary endpoint is evaluation of pain intensity following the implemented procedure. Secondary endpoints are evaluation of anxiolytic effect, achieved level of sedation and observation of possible side effects such as hypotension, bradycardia and desaturation.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness

The risks of prospective collection of demographic data, pain and anxiety scores during and after gas mixture application are negligible and the burden is minimal.

1. INTRODUCTION

Separation of parents, anticipation of unknown procedure and pain related to it create fear and anxiety in children of all ages. Half of admitted children cry, fight with medical staff and panic when preparing for unpleasant procedures like venipunctures, bladder catheterizations, lumbar punctures, bone marrow aspirations, nasogastric tube placement, laceration repairs, and others. One of the most difficult challenges professionally and emotionally is learning to handle pain and stress related emotions in pediatric patients. Pain is defined by the International Association of the Study of Pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage." Expanded definition includes items that provide further context to the complex topic of pain: (1) pain is always a personal experience; (2) pain is different from nociception; (3) pain is learned through life experiences; (4) a person's report of pain should be respected; (5) pain can have adverse effects on function and well-being; and (6) verbal description is one of several behaviors used to express pain.[1] Pain and its' psychological components in children are often under-recognized and undertreated. Children with serious medical conditions as well as healthy children have to undergo significant amounts of painful medical procedures throughout childhood (e.g. vaccinations, venipuncture, heel lance, insertion of a peripheral venous catheter, bone marrow aspirations, lumbar punctures, etc). In the vast majority of infants, no analgesic strategies are employed.[2] Research has shown that exposure to pain and stress related to it early in life has long-lasting consequences in terms of increases in the risk for developing problems in adulthood (chronic pain, anxiety and depressive disorders). Therefore, adequate management of infant and child pain is imperative.[3,4]

Reducing pain and anxiety, avoiding psychological trauma associated with medical procedures are the focus of pediatric anesthesiologist in everyday practice. Nitrous oxide (N2O) is an effective sedative and analgetic agent for mildly to moderately painful pediatric procedures, particularly for short ones.[5,6] It has been used for decades in Europe and USA for pediatric procedural sedation and analgesia (PSA) without serious adverse effects. European Society of Anesthesiology Task Force on Nitrous Oxide issued in 2019. a narrative review concerning use of N2O procedural sedation and analgesia (PSA). This review states that N2O can be efficiently and safely used for procedural sedation in pediatric population for a variety of procedures of light to moderate pain intensity.[7]

2. OBJECTIVES & HYPOTHESES

2.1. Objectives

The aims of this study are:

- to evaluate the efficacy of oxygen: nitrogen 50%:50% gas mixture in achieving analgesia in pediatric patients requiring minor invasive procedures

- to evaluate the efficacy of oxygen: nitrogen 50%:50% gas mixture in achieving desired sedation in pediatric patients requiring minor invasive procedures

- to evaluate safety profile of oxygen : nitrogen 50%:50% gas mixture in achieving desired sedation in pediatric patients requiring minor invasive procedures

Minor invasive procedure investigated in this study are venepunction, arterial line placement, nasogastric tube placement, urinary catheter placement, removal of thoracic drain and kin suture

2.2. Hypotheses

- application of oxygen: nitrogen 50%:50% gas mixture will achieve pain relief in pediatric patients requiring minor invasive procedures

- application of oxygen: nitrogen 50%:50% gas mixture will achieve anxiolysis in pediatric patients requiring minor invasive procedures

3. STUDY DESIGN

Prospective, single center observational study of a random-sample cohort of pediatric patients undergoing any in-hospital minor invasive procedure during a continuous 24 months period of recruitment starting October 2024.

4. STUDY POPULATION

4.1. Population (base)

Pediatric patients undergoing in hospital minor invasive procedures.

4.2. Inclusion criteria

Patients are eligible if:

1 Age 1-16 years

2 Veinpuncture

3 Arterial line placement

4 Nasogastric tube placement

5 Urinary catheter placement

6 Removal of thoracic drain

7 Skin suture

4.3. Exclusion criteria

The following patients will be excluded if any of the following conditions is present

1 Age <1 year or > 16 years

2 Pneumothorax

3 Pneumoperitoneum

4 Pneumocephalus

5 Otitis media

6 Obstructive lung disease

7 Upper airway infection

8 Methylenetetrahydrofolate reductase (MTHF) deficiency

9 Vitamin B12 deficiency

10 Megaloblastic anemia

11 Folate deficiency (Vitamin B9 deficiency)

12 Bleomycin sulphate therapy

13 Neuropathy

14 Pregnancy

4.4. Sample size calculation

Based on previous published data estimated number of patients required to evaluate analgetic and anxiolytic effect as well as safety profile is between 32 and 90.[8,9,10] We aim to observe 300 occasions that required oxygen: nitrogen 50%:50% gas mixture in order to draw unbiased conclusions.

5. METHODS

5.1. Study endpoints

5.1.1. Primary endpoint

Primary endpoint is evaluation of pain intensity using age specific pain scales.

5.1.2. Secondary endpoints:

Secondary endpoints are evaluation of cooperability of a child, anxiolysis, hemodynamic stability during inhalation and oxygenation as well as potential side effects.

Clinical outcome measures:

1 pain assessment as no/mild pain, assessed using age-based pain scales: FLACC up to 4 years, FACES 4-9 years and Numeric Pain Rating Scale 9-16 years;

2 anxiolytic effect defined as child's cooperabiliy, that is executes orders or refuses to execute orders;

2 Level of sedation (desired level would be mild sedation defined as Ramsey score 2)

3 side effects: desaturation, bradycardia, hypotension

4 heart rate (HR), blood pressure (BP), hemoglobin oxygen saturation (SpO_2); monitored before, during and 30 minutes post gas mixture application

Desaturation is defined as $SpO_2 < 95\%$ on room air. Hypotension, hypertension, bradycardia, tachycardia are defined in accordance to age.

6. PROTOCOL

Application of gas mixture will be conducted via suitable face mask, flow calculated to achieve ventilation minute volume (MV) in accordance to age, MV (L/min) = tidal volume (Vt) x respiratory rate (RR).

6.1 Management of side effects:

1 desaturation – supplemental oxygen via face mask

2 hypotension – iv fluids, vasoactive drugs if needed

3 bradycardia – atropine 0,2 mg iv

Important note – side effects such as hypotension, bradycardia are not expected to occur regarding good pharmacodynamic profile of nitrous oxide on cardiovascular system. However, implementing and monitoring these possible effects during the study increases the safety profile of the study

7. STATISTICS

Descriptive statistics will be used to describe baseline characteristics. Categorical variables will be expressed as n (%), continuous variables as median [IQR]. Depending on data distribution parametric or nonparametric test will be used to explain relationship regarding outcome variables.

8. SAFETY REPORTING

8.1. Definition in matter of Pharmacovigilance

8.1.1. Adverse event

An adverse event is an undesirable experience occurring during the administration of a medicine for which the causal relationship with the administration of the medicine does not have to be proven. An adverse event is any unintended and undesirable signal (e.g. abnormal laboratory findings), symptom or disease that is time-related to the administration of a medicine.

A serious adverse event is any undesirable reaction/event with the following results:

Death

Immediate life-threatening situation,

Permanent or significant disability/incapacity,

Requires hospitalization or prolongation of existing hospitalization,

Is a congenial anomaly or birth defect,

Other medically significant condition.

8.1.2. Interaction

Interaction is a change in the pharmacokinetic or pharmacodynamic properties of a medicine caused by the concurrent administration of another medicine, food, or any other substance.

8.1.3. Special situations:

- Overdose is the administration of a medicine in a single or daily dose in an amount that exceeds the maximum recommended individual or daily dose according to the Summary of Product Characteristics and Patient Information Leaflet, including cumulative effects due to overdose.

- Unauthorized administration (Off label use) of a medicine is the administration of a medicine with marketing authorization, that is administered in a therapeutic indication, dosage or manner not listed in the Summary of Product Characteristics, or not approved.

- Abuse of a medicine is the permanent or occasional, intentional excessive use of a medicine followed by harmful physical or psychological effects.

- Medical error is any unintentional error in prescribing, issuing or administration of a medicine by a healthcare professional or patient.

- Occupational exposure to a medicine is the work-related exposure of a person to a medicine.

- Misuse of a medicinal product are situations where a medicinal product is intentionally and inappropriately used not in accordance with the terms of the marketing authorisation

- Lack of efficacy is an effect which is less than the expected action of the Product

8.2. Reporting of adverse effect and special situations

The post authorization safety study sponsor is responsible to fulfill with its legal obligation with regard Pharmacovigilance. Specifically, the sponsor must identify and register the adverse reactions and special situations derived during the study implementation and to report the cases associated with suspected adverse reactions to the Medicines and Medical Devices Agency of Serbia (ALIMS) within the following deadlines:

For serious adverse events: immediately and no later than 15 days from on the day of receipt of the first information

For non serious adverse event: no later than 90 days from on the day of receipt of the first information

The post authorization safety study sponsor will also inform the Marketing Authorisation Holder (MAH) involved about any adverse event or special situation occurred during the implementation of the present study, which is or not associated with a suspected adverse reaction, within 1 working day in written form from on the day of receipt of the first information.

9. ETHICAL CONSIDERATIONS

9.1. Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (revision Fortaleza, Brazil, October 2013), with Good Clinical Practice (GCP).

9.2. Recruitment and consent

The investigator will enroll patients in the study. Informed consent by the patient and/or parents will be obtained by the investigator.

9.3. Benefits and risks assessment, group relatedness

This study does not result in any risk or burdens to patients.

9.4. Incentives

There is no financial incentive for subjects to participate in this study.

References

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