folkehelseinstituttet

Project plan:

Effectiveness and safety of nitrous oxide alone, or in combination with other drugs, as sedation regimen in children

Project number	2015_049
Plan prepared (dd.mm.åååå):	30.08.2017

Short description and summary

Children (up to 18 years of age) who undergo painful procedures at hospitals, for example suture laceration, orthopaedic manipulation, arthrocentesis, insertion of peripheral venous catheters or lumbar puncture, are given different kinds of pain relief (analgesics), often in combination with drugs for relaxation (sedatives). Several drugs are available and chosen depending on procedure, procedure time, effect needed (anxiolytic, sedative or analgesic effect), available personnel and previous experience with the child's responsiveness. Nitrous oxide (N2O) (lystgass) is a drug administered for pain relief and relaxation, it is applied by inhalation and its effects are analgesic, anxiolytic and sedative. It is widely used in maternity wards in Norway for sedation during labour. Our aim is to evaluate the effectiveness and safety of this sedation regimen in children.

Kort beskrivelse/sammendrag

Barn (opp til 18 år) som gjennomgår smertefulle sykehusprosedyrer, for eksempel suturering, ortopediske manipulasjoner, leddpunksjoner, innsetting av veneflon og spinalpunksjon, får forskjellige smertestillende midler, ofte i kombinasjon med avslappende midler (sedativer). Flere legemidler er tilgjengelige og blir valgt ut fra hvilken prosedyre som skal gjøres, hvor lang tid prosedyren er forventet å ta, hvilken effekt man trenger (angstdempende, avslappende, smertestillende eller total bedøvelse), tilgang på personell, samt erfaring med hvordan barnet før har respondert på behandlingen og sedasjonen. Lystgass gis ved inhalasjon og har både smertestillende, angstdempende og beroligende effekt. Det er i etablert bruk på fødeavdelinger i Norge. Vårt mål er å evaluere effekt og sikkerhet av lystgass som sedasjonsmetode for barn.

Short title

Nitrous oxide sedation in children

Project category and commissioner	
Product (program area)	Health Technology Assessment
Thematic areas	Procedure Anaesthetics Sedation Health Technology Assessment
Commissioner:	The Regional Health Authorities Forum (RHA Forum) (RHF-Bestillerforum) (An Ordering Forum, Bestillerforum RHF, consisting of the four medical directors (one for each regional health authority) and two delegates from the Norwegian Directorate of Health, has the mandate to prioritize the STAs and HTAs to be conducted on the basis of submitted proposals and horizon scanning reports.)
Project management and participants	
Project manager	Torunn Elisabeth Tjelle
Responsible for the project	Ingvil Sæterdal von Mehren
Internal project participants	Julia Bidonde Elisabeth Hafstad
External project participants	Karin Tylleskär, Helse Bergen HF, Haukeland Universitetssjukehus Ketil Størdal, Sykehuset Østfold HF
Plan for replacement by project participants' absence	The person responsible for the project will replace the project participants when needed
Internal reviewers	Brynjar Fure, Liv Merete Reinar
External reviewers	To be determined

Glossary

Anaesthetics	Drug to induce insensitivity to pain*
Amnesiacs	Drug to induce memory loss*
Analgesics	Drug for pain relieve without loss of consciousness*
Anxiolytics	Drug to reduce anxiety*
Diffusion hypoxia	Decrease in alveolar oxygen tension caused by inhalation of nitrous oxygen which diffuses out of the blood and dilutes the alveolar oxygen.
Hypnotics	Drug to induce sleep*
Minimal sedation (anxiolytic)	"A drug-induced state during which patients are awake and calm, and respond normally to verbal commands. Although cognitive function and coordination may be impaired, ventilatory and cardiovascular functions are unaffected." (1).
Moderate sedation (conscious sedation)	"Drug-induced depression of consciousness during which patients are sleepy but respond purposefully to verbal commands or light tactile stimulation. No interventions are required to maintain a patent airway. Spontaneous ventilation is adequate. Cardiovascular function is usually maintained." (1).
Sedative	Drug for calming or sleep-inducing effect*

** Definitions are taken from Oxford Dictionary (https://en.oxforddictionaries.com/definition/sedative)*

Mandate

The Regional Health Authorities Forum (RHA Forum) in the national system for the managed introduction of new health technologies within the specialist health service (Bestillerforum RHF) has requested a health technology assessment (HTA) to evaluate safety and effectiveness of nitrous oxide sedation in children. In the note to Bestillerforum-RHF it was suggested that cost effectiveness was not important for the assessment and therefore this is not addressed here.

Goal

To evaluate effectiveness and safety of nitrous oxide sedation regimen in children.

Background

Children (up to 18 years of age) who undergo painful procedures at hospitals, for example suture laceration, orthopaedic manipulation, arthrocentesis, insertion of peripheral venous catheters or lumbar puncture, are offered different kinds of pain relief (analgesics), often in combination with drugs for relaxation (sedatives). For successful procedures, as well as effective use of time and personnel, efforts are made to choose an efficient combination of analgesics and sedatives.

Drugs classified as sedatives may exert one or several effects. Common effects, in addition to the sedative effect, are anxiolytic, amnestic, hypnotic and/or analgesic. The choice of sedatives depends on the procedures to be carried out, procedure duration, effect needed, available personnel and previous experience with the child's responsiveness to the procedure or sedative. The most commonly used sedative at paediatric departments in Norwegian hospitals is Midazolam (2) which can be administered by several different routes (e.g. orally, intramuscular, buccal and nasal spray). Other drugs used for sedative purposes in children are Ketamine, Chloral hydrate, opioid drugs, Propofol and Sevofluorane and nitrous oxide gas. The use of these sedatives have been reviewed by the National Institute for Health and Care Excellence (NICE) guideline in 2010 (3). This guideline recommends to use nitrous oxide and/or Midazolam for sedation in children during painful hospital procedures when the target level of sedation is "minimal" or "moderate", also known as "anxiolysis" or "conscious" sedation, respectively (the definition is established by American Society of Anesthesiologists, ASA (1)).

Nitrous oxide is an inorganic agent, administered by inhalation, colorless, odorless to sweet-smelling, and non-irritating to the tissues. It is an effective analgesic/anxiolytic/sedative agent causing central nervous system depression and euphoria with little effect on the respiratory system. Nitrous oxide has a rapid uptake, as it is being absorbed quickly from the alveoli, and is excreted quickly from the lungs. As nitrous oxide is 34 times more soluble than nitrogen in blood, diffusion hypoxia may occur (4).

Nitrous oxide is used as a sedative in dental care for both children and adults (4;5) and for women in labour (6;7). The gas is normally used with oxygen in different concentrations, the most commonly being 50-70% nitrous oxide (8). Administration is simple and painless and has a rapid onset and short duration of action. It has analgesic, anxiolytic and sedative effects. In Norway it is known as "lystgass" and a popular name in English is "laughing gas" or "gas and air".

Several studies have documented the use of nitrous oxide sedation in children, in particular in the emergency department (9;10). Several guidelines (3;4) include nitrous oxide in their lists of alternative sedation methods in children. A systematic review by Pedersen *et al.* (11) summarize literature on nitrous oxide as a sedation method for minor paediatric procedures for example under peripheral venous cannulations, lumbar punctures or intramuscular injections. The authors concludes that nitrous oxide is a safe and effective method to achieve analgesia and sedation during minor, but painful procedures. The authors therefore suggests that under the right conditions, the use of nitrous oxide will ease hospital procedures which otherwise would be performed using other sedatives that requires longer time, both onset and follow up time, more personnel, or even that it can substitute full anaesthesia.

In Norway, nitrous oxide sedation in children is not a standard sedation method although it is used in some hospitals for minor hospital procedures (St. Olavs Hospital, Trondheim). Also, to our knowledge, there is an ongoing (non-randomized) clinical trial investigating the effectiveness of this sedative (Sykehuset Østfold HF).

This project aims to evaluate and/or synthetize data on effectiveness and safety of nitrous oxide sedation in children, alone or in combination with other sedatives or analgesics.

Methods

We will perform a systematic review on effectiveness and safety of nitrous oxide for sedation in children in accordance with the handbook "Slik oppsummerer vi forskning", by National Institute of Public Health (12). The final report will be written as a systematic review or an overview over systematic reviews, depending on available literature.

We will follow a population, intervention, comparator, outcome and study design (PICO) framework to set parameters for our literature search and study selection. Further steps in this process are search for literature, select studies, assess the methodological quality of the studies, retrieve data, combine data (if possible) and finally assess the certainty of evidence.

Study inclusion and exclusion criteria

Our PICO framework helps the inclusion criteria to evaluate the suitability of studies.

Inclusion criteria

Population	Children up to 18 years of age undergoing painful hospital procedures that require minimal or moderate sedation
Intervention	a) Nitrous oxide only b) Nitrous oxide in combination with other sedatives/analgesics/anaesthetics* Nitrous oxygen/oxygen concentration: 50/50% – 70/30%
Control	a) Other pharmacological intervention (sedatives/analgesics/anaesthetics) b) Non-pharmacological intervention (e.g. psychological techniques) c) Control (wait list, treatment as usual) (For safety outcomes we will accept studies without any control group)
Outcome	a) Hospital procedure satisfaction (e.g. easiness, distress, anxiety) b) Hospital procedure characteristics (e.g. successful procedural completions, number of attempts, duration of procedure) c) Pain d) Safety of sedation - Number of acute adverse events (e.g. vomiting, oxygen desaturation, cardiac arrest) - Long term adverse effects (e.g. toxicity) due to repeated exposure - Parameters of gas concentration in the procedure room or body - Adverse events due to combination with other sedatives/ analgesics/ anaesthetics For each of the outcomes, we will extract data provided either by the patient (child), caregiver (parent) or health personnel (medical staff).
Study design	Systematic reviews, of high methodological quality, of randomized controlled trials, health technology assessments (HTA) or randomized controlled trials. If

required, non-randomized studies (Non-randomized controlled trials, Controlled before-and-after study, Prospective cohort study, Retrospective cohort study, Case-control study (more than 50 participants), Case report/Case series (more than 100 participants) will be included for data on safety. We will only include published studies that assessed any of the predefined outcomes.

** For data on nitrous oxide in combination with other drugs we will only present it as such and not analyse effects or safety of the individual drug.*

Exclusion criteria

We will exclude studies based on:

- Patient groups using nitrous oxide for sleeping disorders
- Imaging procedures or procedures only requiring the sleeping effect
- Procedures where the aim is to obtain general anaesthesia
- Animal studies

Search strategy

We will primarily search for systematic reviews and HTAs. If this is not found, or if the systematic reviews are older than 5 years, randomized controlled trials will be used, either alone or to supplement the systematic reviews. If necessary for acquiring enough data on safety, we will conduct separate searches for non-randomized studies. The relevant databases to be searched are listed below.

Systematic reviews & HTA

- CRD database, HTA (Centre for Reviews and Dissemination, University of York)
- Cochrane Library (Wiley):
    - Cochrane Database of Systematic Reviews
    - Database of Abstracts of Reviews of Effects
- Epistemonikos
- Embase (OVID)
- PubMed (NLM)

Randomized controlled trials (and non-randomized studies, if required)

- Cochrane Central Register of Controlled Trials (Wiley)
- PubMed (NLM)/MEDLINE (OVID)
- Embase (OVID)

Ongoing, completed or terminated (unpublished) trials

- Clinical Trials (National Institutes of Health, US)
- International Clinical Trials Registry Platform (WHO)

An information specialist, in collaboration with the research team, will plan and conduct the searches. The search strategies will combine index terms and text words relating to population and intervention, adapting the search syntax to each database. Filters for study design will be added for databases PubMed/MEDLINE and Embase.

The research team will examine the bibliographies of included articles for relevant titles not identified by the searches.

Selection of studies

The team will select articles following a two-step strategy. Both steps will be carried out considering inclusion and exclusion criteria detailed above. Disagreement at either stage will be settled by discussion or consultation with a third person.

Selection strategy:

1. Two reviewers will independently assess title and abstracts of retrieved articles to determine relevant full-text articles to be examined
2. Subsequently, two reviewers will independently assess the full-text articles to decide which articles will be included in the systematic review.

Assessment of methodological quality and risk of bias

We will evaluate the quality (risk of bias) of the identified trials using the Cochrane tool (http://training.cochrane.org/handbook, Chapter 8.5a). For non-randomized studies we will use the checklists given in our handbook (12). Two review authors will assess the quality of the included studies independently. We will resolve disagreements by discussions or, if required, by consulting one of the other review authors.

Data extraction and analyses

One review author will extract data from the included studies and another review author will verify the data. We will extract the following data:

- Information about the study (authors, year of publication, setting, study design, clinical trial identification number and funding source)
- Participant characteristics (number of participants in the trial, age, procedure to be performed during intervention)
- Intervention and control characteristics (combination of drug, doses, length of exposure, frequency of intervention per patient)
- Outcomes (endpoints examined, methods used to analyse outcome data, length of follow up and loss to follow up)

Statistical analyses

We will synthetize the outcomes depending upon the research design.

For all outcomes, we will present the results in summary of finding tables.

For Randomized Controlled Trials: If homogenous randomized controlled trials are found, effect sizes will be combined in meta-analyses. Continuous data will be expressed in the form of mean difference (MD) or standardized mean difference (SMD) and 95% confidence interval (CI), and Dichotomous data will be analysed by calculating relative risk (RR) and the

corresponding 95% CI. Outcomes which cannot be combined, will be presented in a narrative form.

If relevant or if possible, we will divide the data in groups and analyse them separately based on the setting (which department, which personnel), age of patient, hospital procedure performed, and if nitrous oxide is used in combination with other sedatives/ analgesics/ anaesthetics.

Grading the certainty of evidence

Two review authors will independently assess the certainty of the evidence for each selected outcome using the GRADE system (Grading of Recommendations Assessment, Development, and Evaluation, http://www.guidelinedevelopment.org/). We will do this to ascertain the strength of the study design, possible risk of bias, imprecision and inconsistency of the estimates, and indirectness and magnitude of effect, dose response gradient and potential confounding factors. The GRADE system classifies the certainty of the evidence as high, moderate, low, or very low for each outcome, described in the table below.

Table: Definition of each category for GRADE

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Norwegian Institute of Public Health review process

We follow the process of Norwegian Institute of Public Health where two external clinical experts and two internal research directors are invited to review and give feedback on the project plan. The plan will then be approved by the management group of the HTA-unit (KO-ledermøtet) before publication at NyeMetoder.no. The final report will be reviewed by another two external experts together with the same two internal research directors. Subsequently it will be approved by the HTA-unit before submission to the commissioner. Publication (https://nyemetoder.no/metoder), will be done latest 10 days after submission to the commissioner.

Activities and schedule

Following activities are planned in the project:

- Find and include external reviewers

- Discuss project plan with internal and external reviewers
- Approval of project plan
- Search for literature
- Select studies according to inclusion/exclusion criteria
- Evaluate methodological quality (RoB)
- Extract data on efficacy and safety and conduct statistical analyses
- GRADE evaluation for each outcome
- Write and review the draft report
- Approve and submit the report

Date for commision

27. February 2017

Start date (for FHI.no)

10. June 2017

End date

27. February 2018

Publication / dissemination

The end product will be a report from Division of Health Services, Norwegian Institute of Public Health, under Nye Metoder (https://nyemetoder.no/metoder), and possibly as a scientific article.

Indexing for web page

Adolescent, Anaesthesia, Analgesia, Child, Conscious Sedation, Infant, Minor Surgical Procedures, Nitrous Oxide, Anti-Anxiety Agents, Hypnotics and Sedatives

Internal pediatrics related projects/publications

There are no related ongoing projects or related publications published from Norwegian Institute of Public Health.

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