Trials

STUDY PROTOCOL

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Efficacy of virtual reality hypnosis versus conscious sedation with nitrous oxide in the management of dental anxiety in pediatric dentistry: protocol for a prospective randomized controlled trial

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Abstract

Background Dental anxiety is defined as a persistent and excessive fear of dental treatment. It often leads to interruptions during procedures and, frequently, avoidance of dental care. For patients over the age of 7, nitrous oxide-oxygen inhaled sedation (NOIS) represents one of the most effective and well-established pharmacological approaches to reducing anxiety and pain during dental treatment. Meanwhile, medical hypnosis offers an interesting non-pharmacological alternative by inducing a hypnotic state, potentially serving as a means of sedation to alleviate anxiety or pain. The advancement of virtual reality (VR) technology makes medical hypnosis more accessible to dental practitioners, yielding promising outcomes. To our knowledge, no clinical trial has evaluated the efficacy of medical hypnosis associated with 3D immersive virtual reality devices for pediatric dental procedures.

Methods This prospective, controlled, single-blind clinical study including anxious patients aged 7 to 10 years old aims to demonstrate non-inferiority of virtual reality approach. Using a split-mouth design, each patient will attend two separate visits for two comparable conservative dental procedures. At the first procedure, they will randomly be assigned to receive either hypnosis via VR or NOIS. The alternative method will be administered during the second visit. The primary outcome is the sedation success based on the completion of the dental procedure. A score of 3 or higher on the Modified Venham Scale noted more than twice ends the session and qualifies as a sedation failure. The secondary outcomes involve assessing children's tolerance and the temperament influence on sedation success.

Discussion This study will evaluate the efficacy of a novel non-pharmacological sedation for the management of anxious children in a dental setting. The results may help practitioners choose the appropriate anxiolytic therapeutic option, based on different psychometric and temperament parameters.

Trial registration ClinicalTrials.gov NCT05167331. Registered on December 22, 2021.

Keywords Dental anxiety, Hypnosis, Virtual reality, Nitrous oxide, Conscious sedation, Child behavior

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Background

Dental anxiety and dental pain are significant factors leading to agitation and lack of cooperation among children in dental settings [1]. These challenges, referred to as dental behavior management problems (DBMP), often result in treatment interruptions and reluctance to seek pediatric dental care [1]. Addressing children's anxiety towards dental treatment is essential not only to reduce immediate fear but also to prevent long-term apprehension into adulthood [2]. Failure to do so can contribute to long-term avoidance of dental care, potentially exacerbating oral health issues [2]. Moreover, dental fear, anxiety, and DBMP are not only linked to negative dental experiences but also associated with poorer oral health outcomes and an increased risk of dental caries [3]. Patients exhibiting DBMP often require more time and specialized approaches during treatment, which could create stressful and challenging experiences for both the child and the dental care team [3].

Between 24 and 30% of preschoolers, as well as roughly 27.6% of schoolchildren worldwide, are reported to experience dental fear based on the majority of clinical and epidemiological studies available [4, 5]. Interestingly, the children who have not had previous dental visits and those with dental caries are more prone to experiencing dental fear [4]. Additionally, there is no significant difference in the prevalence of dental fear between boys and girls [5].

To manage these children, cognitive therapies and behavioral approaches alone may often be insufficient. Depending on the clinical situation, practitioners may resort to a continuum of sedation. For anxious patients over the age of 5, the recommended pharmacological sedation is nitrous oxide-oxygen N_2O/O_2 inhaled sedation (NOIS) [6, 7]. The primary desired effect is a slight alteration of consciousness, making patients less alert to their surroundings [7]. Additionally, it lowers the threshold for perceiving various painful stimuli; however, its analgesic effect remains minor and superficial. Concerning the pharmacological and metabolic aspects, the rapid pulmonary absorption and elimination of nitrous oxide occur due to its low solubility in blood and tissues, leading to quick induction and recovery times [7]. According to the European Academy of Paediatric Dentistry and the American Academy of Pediatric Dentistry, conscious sedation through N_2O/O_2 inhalation is an effective and safe therapy for reducing anxiety and providing comfort during treatment [6, 7]. A recent systematic reviews and meta-analysis estimated the efficacy rates of NOIS for pediatric populations during dental procedures at 91.9% (95% CI: 82.5–98.2%) [8].

In line with practices in several other European countries, the Equimolar Mixture of Oxygen and Nitrous Oxide (EMONO) is the only formulation available in France for dental care. The EMONO therapeutic value was deemed important by the Haute Autorité de Santé, the French authority in charge of the regulation of the health care system. Recent studies have shown the efficacy and safety of such combination for dental care.

Adverse effects, observed in approximately 0.5–1.2% of patients, primarily include nausea and vomiting [9]. This incidence tends to rise with prolonged exposure to N_2O/O_2, fluctuations in nitrous oxide levels, absence of proper titration, higher concentrations of nitrous oxide, and consumption of a substantial meal before nitrous oxide administration [10]. Additional adverse effects may include oversedation, sweating, dysphoria, restlessness, panic, and headache, as well as dizziness, hallucination, diffusion hypoxia, and expansion of gas-filled spaces [10]. These effects have been documented alongside the administration of nitrous oxide. Research on the occupational exposure of dental personnel to ambient nitrous oxide has been ongoing for decades, although the specific effects remain unclear [11]. Initial findings, often from retrospective or animal studies predating the implementation of scavenging devices and ventilation systems, suggested potential risks associated with chronic exposure to unscavenged nitrous oxide, including reproductive effects, liver and kidney damage, and neurological concerns [11].

Furthermore, it is one of the main greenhouse gasses. The biotransformation and biodegradation of nitrous oxide are very slow, and the gas's half-life in the atmosphere is estimated to be between 100 and 150 years [12]. It destroys the ozone layer that protects us from the sun's ultraviolet radiation. Additionally, it contributes to the greenhouse effect, acid rain, and, like CO_2, leads to global warming. Nitrous oxide of medical origin accounts for approximately 10% of atmospheric pollution [12].

While the ecological argument may dissuade some from using nitrous oxide, its significance diminishes in situations where its use is necessary. However, exploring and assessing alternative approaches for managing anxious children would be beneficial to provide options other than nitrous oxide inhalation in dental practices.

An alternative therapy worth considering is medical hypnosis. This notable approach involves the practitioner inducing a distinct state of consciousness in the patient through verbal communication. This state is characterized by a detachment from the external environment and increased susceptibility to suggestions. Termed as altered consciousness or a "hypnotic" state, it can serve purposes such as sedation (hypnosedation), anxiety reduction, or pain management (hypnoanalgesia). More than 300 randomized controlled trials and over 80 systematic reviews or meta-analyses are indexed in the MEDLINE database

under the keyword "hypnosis [MeSH Major Topic]." Among them, a recent systematic review has been published in the Cochrane Database, assessing the effects of methods for acceptance of local anesthesia in children and adolescents during dental treatment [13]. The authors' conclusion suggests that psychological interventions, particularly distraction, hypnosis, and combined cognitive-behavioral approaches, can yield positive results [13]. Similar to this systematic review, several randomized studies have demonstrated the benefits of hypnosis induction prior to local or regional anesthesia and surgery: pain scores, incidence of nausea and/or vomiting, as well as the consumption of morphine and sedatives, were significantly lower in the treated group [14]. Hypnosis also exhibits anxiolytic effects regardless of the patient's age [15]. Three fundamental conditions remain essential in hypnosis: patient motivation, patient cooperation, and patient trust in the therapist.

Nevertheless, the implementation, indications, and use of hypnosis face limitations due to various factors, including the expertise and background necessary in hypnosis, the time and effort necessary for practitioners who perform hypnosis, and the cognitive effort required by patients to undergo hypnosis. The emergence of new technologies such as virtual reality helps simplify hypnotic induction through immersive multisensory three-dimensional experiences. Research has demonstrated the value of virtual reality in pain management and stress reduction [16]. Hoffman et al. compared the effectiveness of SnowWorld, a virtual reality game, to opioid analgesics for pain management [17]. The use of virtual reality gaming, combined with analgesic treatment, significantly reduced pain intensity compared to morphine treatment alone. Multisensory immersion in virtual reality also helps alleviate anxiety and focus attention on the scenario [18]. Studies have shown that virtual reality is more effective than video games or movies, which are sometimes used as therapy in hospitals [16, 18].

Combining medical hypnosis with virtual reality could prove beneficial by leveraging the advantages of both techniques and capitalizing on their synergy in assisting anxious children.

Objectives

The aim of our clinical study is to assess the HYPNO-VR device, comprising a three-dimensional virtual reality visual scenario synchronized with conversational hypnosis discourse. The visual immersion and hypnotic speech are respectively delivered through virtual reality goggles and an audio headset to accompany the patient during dental procedures. This approach aims to guide the patient through the same stages of hypnosis as when induced by a traditional hypnotherapist. To our knowledge, no other publication has proposed the use of virtual reality devices with medical hypnosis scenarios for dental procedures in children.

The primary objective will be establishing the non-inferiority of virtual reality compared to a standard pharmacological sedation (EMONO) in managing dental anxiety in children.

Secondary objectives include examining the analgesic potential of virtual reality, comparing patient satisfaction between virtual reality and medication, evaluating children's tolerance to both methods, and studying how the child's temperament affects their acceptance of virtual reality and responsiveness to hypnotic suggestions.

Methods and design

The clinical trial protocol is identified as version number 1.2 of 23rd of August 2021. It adheres to Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) criteria; the SPIRIT Checklist can be found as Additional file 1.

Trial design and blindness

This non-inferiority, prospective, randomized, controlled, single-blind, split-mouth two-group study will be conducted in the pediatric subunits of the Department of Oral Medicine and Surgery of the Strasbourg University Hospital.

The working hypothesis of this study is that hypnosis through virtual reality can reduce children's anxiety, as well as their pain level during dental care with an efficiency and tolerance at least similar to nitrous oxide inhalation. Specifically, the statistical analyses will be based on an assumption of non-inferiority of VR compared to the pharmacological technique of nitrous oxide sedation.

Each patient (aged from 7 to 10 years old) attends for two visits in order to benefit of 2 similar conservative dental treatments on primary molars.

Everyone was randomly allocated to receive hypnosis through virtual reality or nitrous oxide/oxygen titrated to 50%/50% at the first visit, the alternative being used at the second visit (Fig. 1). This randomization helps avoid any experimental bias related to a first positive or negative experience, each patient being its own control, adjusting for potential confounders.

Vital signs and a video of the child's behavior are recorded for an external examinator (Fig. 1). The video shows the child's body response as an indicator for his anxiety level through the procedures. Given the nature of both devices, an open-label protocol is inevitable; the investigator as well as the patient is aware of the device used. To reduce the risk of bias, we propose to hide the child's face in the treatment videos. Therefore,

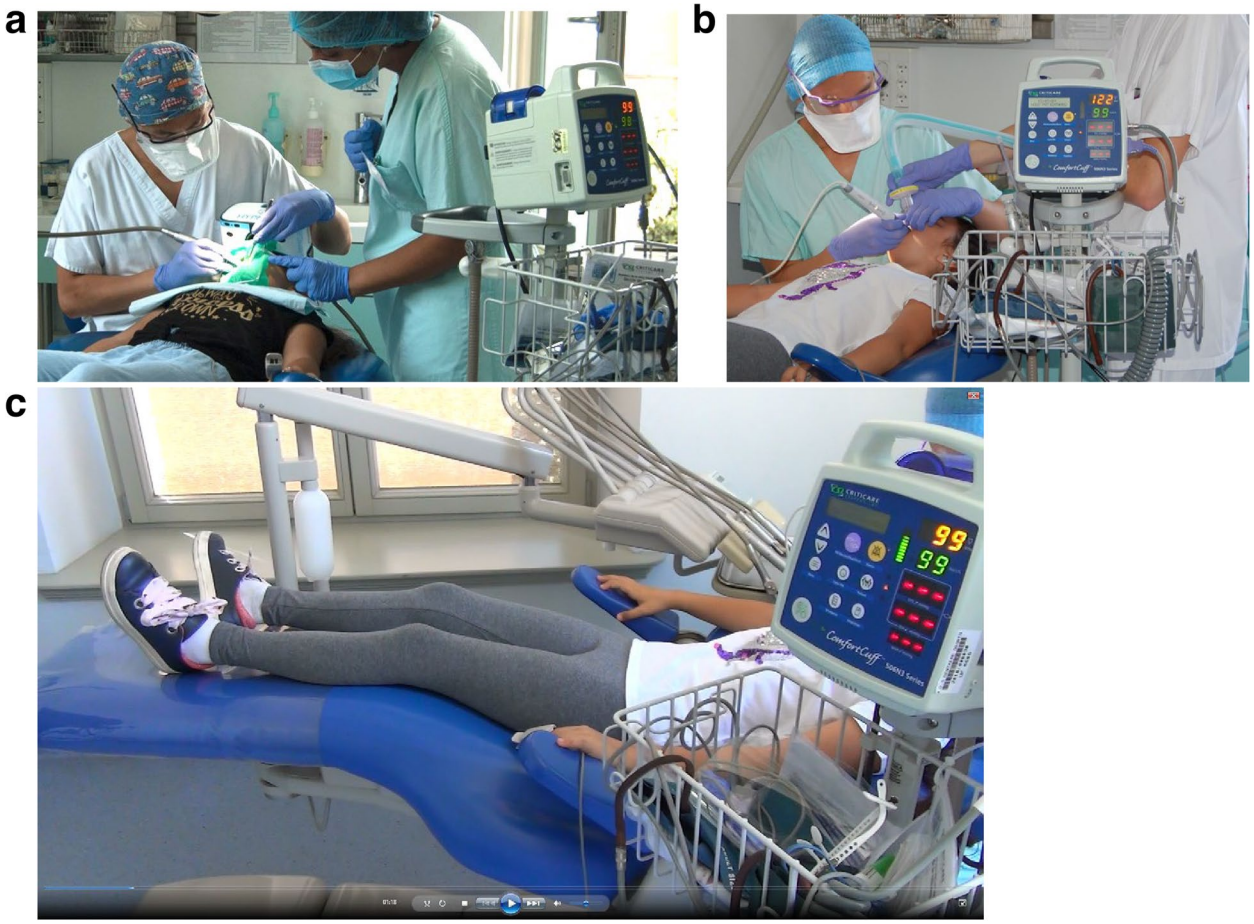

Fig. 1 **a** Session using virtual reality goggles; **b** session using EMONO; **c** videos viewed by the outcome examinator who can be blinded in order to reduce risks of bias

the external evaluator will be unaware of the device (EMONO or VR) during the assessment of the child's behavior (Fig. 1). We will also blind the statistician supervising the analyses. It is not possible, however, to blind patients and operators.

A pilot study conducted in our department in 2020 focuses on the tolerance and effectiveness of HypnoVR program in our everyday practice and the clinical feasibility of this study protocol. This pilot study primarily includes anxious young patients, aged 7 years and older. It rehearses the recruitment, randomization, allocation, documentation, and sedation procedures according to this protocol. In this phase, eight patients were recruited; however, they will not be included in the group of participants of the final sample.

Involvement in the design of the protocol

No members of the public or patient groups were involved in the design of the protocol.

Randomization

The chosen study design is a crossover study; the experimental design model is split-mouth with both sedations being administered to the same patient during two consecutive treatment sessions. Therefore, the results of the first session may positively or negatively influence the outcome of the second session. After confirming the inclusion criteria, randomization will be conducted to determine the sedation order and teeth to be treated for each session. The first group of children will start treatment with EMONO, while the other group will begin with VR.

Concerning the methodology, randomization will be done using random block sizes with random patient allocation. Utilizing variable block sizes randomly defined with sequence permutation allows for better unpredictability. The risk of investigator anticipation of allocation is minimal since the block sizes vary.

The randomization list will be established by the Group of Methods in Clinical Research of Strasbourg.

Randomization will occur via internet, using the Cleanweb platform, after obtaining informed consent during the inclusion visit.

Study population

The participants and dental eligibility criteria are described in Table 1. The patients are referred by their former dentist because the patients experienced dental anxiety during a previous session and could not complete the intervention. Dental exclusion criteria have been chosen to reduce failure that is independent of the treatment studied. No emergency dental care, if needed, is prohibited in children after inclusion in the trial.

Outcomes

The primary outcome of this trial is the assessment of the anxiety levels using the Modified Venham Scale (MVS) and the Face Legs Activity Cry Consolability (FLACC) scale (Tables 2 and 3). Both are standardized hetero-evaluation devices to evaluate the child's behavior and anxiety level during the procedure. MVS is a scale ranging from 0 (patient completely calm and relaxed) to 5 (patient in distress, completely disconnected) and FLACC ranging from 0 to 8. In our study, the category Face will not be used since the patient's face is not visible in the video. Several parameters are considered in these scales, such as the child's movements, crying or screaming, and the ability to perform the procedure. These scales are reliable, easy-to-use, and reproducible tools for evaluating children's behavior.

Success of the sedation can be defined by the completion of the dental procedure. A Venham score of 3 or more, noted at two different timepoints, requires the end of the session and therefore the failure of the sedation.

The secondary outcomes include:

- Evaluation of analgesia through self-reported pain levels on the Visual Analog Scale (VAS) combined with Wong-Baker's FACES scale, standardized age-appropriate scales, and through monitoring vital signs during the procedure.
- Assessment of tolerance and response to VR and EMONO through the number and proportion of patients intolerant to VR and pharmacological techniques. Evaluate the proportion of VR or EMONO sessions interrupted (lack of therapeutic continuity). Patients who interrupted VR more than once or refused VR during the intervention session are considered intolerant to VR.
- Assessment of child temperament using a questionnaire and temperament scale (Emotionality Activity Sociability (EAS) questionnaire) [19].

To assess the temperament dimensions of the child, parents complete an Activity, Emotionality, and Sociability (AES) questionnaire with the assistance of an

Table 1 Eligibility criteria

Inclusion criteria:
- Patients aged between 7 and 10 years old
- Patients with indications for dental treatment (conservative and/or endodontic) in at least 2 temporary molars belonging to the same dental arcade, contralateral (fractional mouth), and equivalent in terms of carious lesions and symptoms
- Patients referred by their former dentist because they could not complete the intervention (they would need to disclose the Venham score from the last treatment session)
- Child and parents/legal guardians speak French
- Consent of parents/legal guardians
- Physical status classification from the American Society of Anesthesiologists (ASA): ASA I patients

General exclusion criteria:
- Patients with a history of EMONO or virtual reality sedation for dental treatment
- Patients refusing to undergo preoperative intraoral radiographic examinations
- Patients allergic to local anesthesia
- Contra indications to EMONO:
  - Intracranial hypertension or any alteration in consciousness or facial trauma
  - Risk of increased pressure in closed cavities: gas embolism, emphysema bubbles, gas distension, intestinal gas distension, pneumothorax, Eustachian tube obstruction
  - Repeated upper airway infections
  - Patients with severe psychoses or other severe psychiatric disorders
- Patients with a history of postoperative nausea, vomiting, or motion sickness
- Contra indications to VR:
  - Patients with dementia or developmental delay, psychosis, or under treatment for a psychiatric disorder
  - Patients with history of uncontrolled epilepsy
  - Patients with visual and/or auditory impairments
- Patients with psychiatric disorders or who have taken psychotropic medications within 8 weeks prior to the first visit and during the study period
- Patients with claustrophobia
- Patients not affiliated with a social security health insurance scheme
- Lack of consent from the subject and/or legal guardians to participate in the study

Table 2 FLACC Face Legs Activity Cry Consolability Scale. Each of the five categories (F) Face, (L) Legs, (A) Activity, (C) Cry, and (C) Consolability is scored from 0 to 2, which results in a total score between 0 and 10. 0 = Relaxed and comfortable; 1–3 = mild discomfort; 4–6 = moderate pain; and 7–10 = severe pain or discomfort or both. In our study, the category Face will not be used since the patient's face is not visible in the video

	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn or disinterested; appears sad or worried	Consistent grimace or frown; frequent/constant quivering chin; clenched jaw; distressed-looking face; expression of fright or panic
Legs	Normal position or relaxed; usual tone and motion to limbs	Uneasy, restless, tense; occasional tremors	Kicking, or legs drawn up, marked increase in spasticity, constant tremors or jerking
Activity	Lying quietly, normal position, moves easily; regular and rhythmic respirations	Squirming, shifting back and forth, tense mildly agitated, shallow, splinting respirations intermittent sighs	Arched, rigid, or jerking, severe agitation, head banging, shivering; breath-holding, gasping or sharp intake of breath, severe splinting
Cry	No cry/verbalization	Moans or whimpers, occasional complaint, occasional verbal outburst or grunt	Crying steadily, screams or sobs, frequent complaints, repeated outbursts, constant grunting
Consolability	Content or relaxed	Reassured by occasional touching, hugging, or being talked to, distractible	Difficult to console or comfort, pushing away caregiver, resisting care or comfort measures

investigator before the care session [19]. The AES questionnaire, which has already been validated in France for children aged 6 to 12 years in 2002 [20], consists of 25 items based on a model of three main dimensions: Activity, Emotionality, and Sociability. Each item has a Likert scale ranging from 1 (extremely untrue, not at all like my child) to 5 (extremely true, exactly like my child) [21].

In addition to the child's temperament questionnaire, additional questions related to the child's sociability and artistic and sports development will be proposed to the parents. These questions are aimed at evaluating the impact that extracurricular social, artistic, and sports development has on the child's cooperation at the dental office.

❖ Does the child participate in extracurricular activities in a group setting?

- ○ Is it a sports activity?
- ○ Is it an artistic activity?

❖ For all extracurricular club activities combined, what is the frequency?

- ○ Less than once a week
- ○ Between 1 and 2 times a week
- ○ More than 2 times a week

Recruitment procedures

Participants will be recruited in the pediatric subunits of the Department of Oral Medicine and Surgery of the Strasbourg University Hospital. The participant's timetable is shown in Fig. 2. And the flow chart of the study is shown in Fig. 3.

Interventions

During the enrolment, the initial examination is performed by dental students, supervised by a senior practitioner. During the initial consultation, following clinical and radiographic examinations, a diagnosis of the lesions

Table 3 Modified venham scale MVS

Score 0	Relaxed	Smiling, willing, able to converse, display behavior desired by the dentist
Score 1	Uneasy	Concerned, may protest briefly to indicate discomfort, hands remain down or partially raised. Tense facial expression, high chest. Capable to cooperating
Score 2	Tense	Tone of voice, question and answers reflect anxiety, during stressful procedure, verbal protest, crying, hands tensed and raised, but not interfering very much. Protest more distracting and troublesome. Child still complies with the request to cooperate
Score 3	Reluctant	Pronounced verbal protest, crying. Using hands to stop procedure. Treatment proceeds with difficulty
Score 4	Very disturbed	General crying, body movements sometimes needing physical restraint. Protests disrupt procedure
Score 5	Totally out of control	Hard loud crying, swearing, screaming. Unable to listen, trying to escape. Physical restraint requires

	STUDY PERIOD			
	ENROLMENT	RANDOMIZATION	POST-RANDOMIZATION	
TIMEPOINT	Selection Information	Inclusion Randomization	Intervention I1	Intervention I2
	T0 - 1 week	T0	T0 + 1-2 weeks	V1 + 1-2 weeks
ENROLMENT :				
-selection criteria (individual and teeth)	X			
-informed consent				
-randomization		X		
		X		
INTERVENTION :				
-first treatment			X	
-second treatment				X
ASSESSMENTS :				
-video recording			X	X
-anxiety assessment Venham score		X	X	X
-FLACC score assessment			X	X
-pain assessment VAS scale			X	X
-vital signs monitoring			X	X
-temperament questionnaire		X		

Fig. 2 Schedule of enrolment, interventions, and assessments during the trial

and a treatment plan will be established. Motivation for oral hygiene and dietary habits, as well as prophylactic measures, are carried out. If the study inclusion criteria are met, an information sheet about objectives, methods, follow-up, risks, and restrictions of the trial will be explained and provided to the child and their legal guardians. An appointment will be scheduled with one of the investigators for an informational consultation and consent collection. A minimum reflection period of 1 week will be granted between this initial consultation and the inclusion consultation.

During this second visit, the objectives are to obtain consent after verifying the inclusion and exclusion criteria. It is also important to clearly identify, at this stage, the teeth for which treatment will be scheduled for the study. Then, compliance with oral hygiene and dietary habits are assessed and scaling/polishing and local fluoride application are performed. The "Tell Show Do" psycho-behavioral approach techniques will be used. This approach allows the child to become acquainted with the operating practitioner in a less stressful environment since the procedures are non-invasive. During this session, the investigator will show the child the virtual reality headset equipped with the HYPNO-VR software, which the child can handle and try on to adjust the size of the headset. Subsequently, the child will watch a video presenting various virtual reality scenarios and will choose a universe tailored to their preferences and sensitivity for the intervention session. It is essential for the patient to be able to test

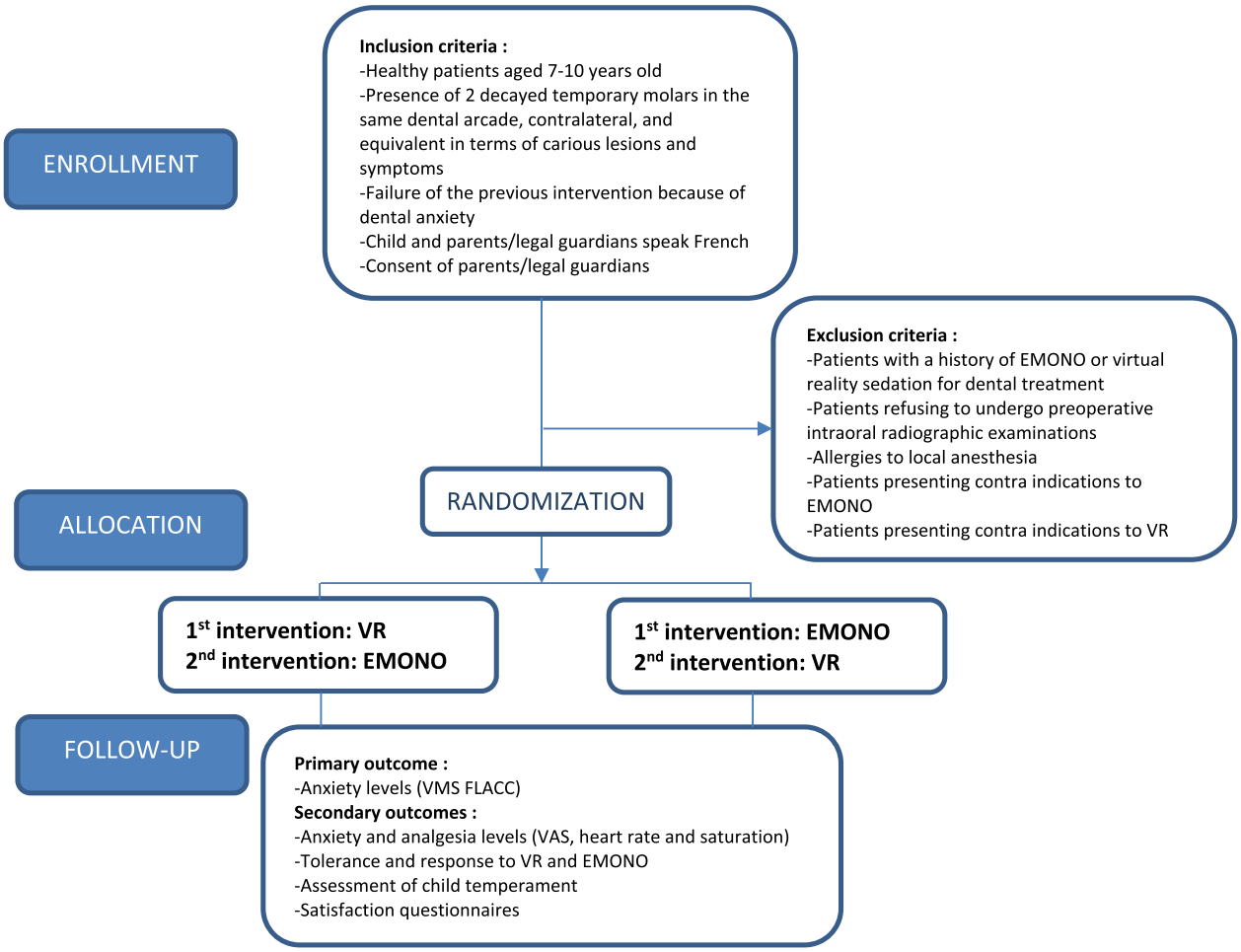

Fig. 3 CONSORT flow diagram of recruitment of subjects, randomization, allocation, completion of local anesthesia administration, and analysis

the device before the treatment sessions because during the intervention, two of the child's five senses will be engaged by virtual reality, thus disconnecting them from the external environment (sight and hearing). Common failures of virtual reality found in the literature include refusal to wear the headset. EMONO masks will also be shown to the child, and the size will be chosen based on the child's face and morphology. The temperament questionnaire will be conducted during this second consultation.

During the treatment sessions, upon the patient's arrival, vital signs are recorded by the investigator (oxygen saturation and heart rate).

- (T0) The patient is then settled in the treatment room, and sedation can be initiated (T1).
- EMONO session: with a mask tailored to the size of their face and the EMONO debit adjusted to their ventilation rate. The assistant is responsible for monitoring sedation. Verbal reassurance is consistently provided to comfort the child.
- VR session: after adjusting the visual and audio headset on the child's face, the assistant starts the VR program chosen by the child.
- (T2) Five minutes after induction, intraosseous computerized local anesthesia with the QUICKSLEEPER device is administered. An intraosseous injection of one anesthetic capsule Articaine SEPTANEST 1/200,000 is performed.
- (T3) After placing the dental dam, the investigator proceeds with restorative ± endodontic treatment of the selected primary molar.
- (T4) Once the treatment is completed, sedation is discontinued, and the patient rests in the chair for 5 min.
- (T5) As soon as the investigator deems the child to be back to normal, they can leave the office with their parents.

Throughout the session, video recording of the child's position and body language is conducted for external evaluation of the child's behavior during sedation. The Venham score, FLACC score, and vital signs are recorded at T0, T1, T2, T3, T4, and T5.

During the VR session, the patient is first placed in a relaxation room, where a preliminary virtual reality hypnosis sequence aimed at relaxation is initiated for 10 min. This preliminary step before treatment allows the child to become accustomed to the headset and to be prepared for the dental procedure under virtual reality.

The enrollment of participants and the interventions are carried out by a single investigator (N.M.D.) (Fig. 3).

Assessment and calibration of the examinator

An audio/video recording is conducted during the treatment sessions for behavior assessment by a single external examinator. There can be variations in scoring criteria across researchers and even over time by a single researcher.

In order to obtain an objective assessment of anxiety based on the Venham and FLACC scales, prior training and calibration of the external examiner were conducted using a group of 8 patients during the pilot study.

To reinforce the intra-examinator reliability of the tools, video assessment was done twice by the same examinator, at least 5 months apart, and after a second randomization of the videos.

Data management

The baseline data, follow-up trial data, and adverse events will be recorded by operators and evaluators on case report forms (CRFs). Data will be kept anonymous. Patients will be identified by their inclusion data; only the number of the patient and the initial letter of their first and last name will be registered on the CRF.

Determination of sample size

The minimally required number of participants to include was calculated based on the primary outcome (level of anxiety and child behavior during sedation) through simulations. For this purpose, data from various clinical studies were considered to estimate the sample size and the following assumptions were made [22–26]:

- Under pharmacological sedation using EMONO, 30% of subjects will have a Venham score of 2, 50% will have a score of 3, and 20% will have a score of 4.
- 30% of subjects will not experience any change in their score.
- Among the subjects who experience a change in their score, 20% will have a decrease of 1 point, 50% will have a decrease of 2 points, and 30% will have an increase of 1 point.

These hypotheses are closed to the hypotheses used to the sample size estimation by Salam et al. (VR group: 2.25 ± 0.89 and control group 3.50 ± 1.31).

A total of 30 subjects will achieve a power of 90% and a type I error rate of 5% to detect a mean score with VR that is not more than 0.1 point higher than the mean score with EMONO.

Statistical analysis

The statistical analysis will consist of both descriptive and inferential parts. Statistical analyses will be conducted using Bayesian methods.

Descriptive statistical analysis of quantitative variables will involve presenting the entire set of observed values (univariate analysis), including the frequency of each value and its relative frequency. These frequencies will be provided individually and in cumulative form. For each variable, measures of central tendency (mean, median), measures of dispersion (variance, standard deviation), and measures of distribution (minimum, maximum, first and third quartiles) will be reported. The normality of the data will be assessed using the Shapiro–Wilk test and quantile–quantile plots. Descriptive analysis of qualitative variables will involve presenting frequencies and proportions of each category in the sample. Cross-tabulations will be provided, including frequencies, row proportions, column proportions, and proportions relative to the total, as necessary.

To address the primary objective, inferential analysis will compare Venham scores between subjects receiving VR and those with EMONO inhalation through paired mean comparisons. For secondary objectives, paired mean and proportion comparisons will be conducted. Bayesian linear regressions will be performed to examine changes in anxiety and pain levels over iterative sessions.

The prior distributions will be minimally informative or informative for sensitivity analysis purposes. For each analysis, the posterior distribution of the parameter of interest (proportion, mean, regression coefficient, etc.) will be estimated using the Markov Chain Monte Carlo method. The default number of iterations will be 100,000 after discarding the first 10,000, retaining every second value (thus, 210,000 iterations will be conducted). Convergence will be assessed graphically, and autocorrelation will be estimated graphically. If necessary, the number of iterations will be increased to reduce autocorrelation.

The analyses will be conducted using the R software in its most current version at the time of analysis, along with any necessary packages, and with the OpenBUGS and JAGS software.

Protocol violations

All protocol violations occurring after randomization will be listed in the clinical report form (CRF) and tabulated by the subject. The final assignment of participants to the per-protocol analysis will be decided at a blinded protocol review meeting before locking the database.

Ethical consideration

The French ethical committee for the protection of persons (Comité de Protection des Personnes (CPP), Sud Méditerranée III) granted approval in September 2021 (2021-A00033-38). The protocol is registered under the IDRCB (2021-A00033-38) with the French National Agency for Medicines and Health Product Safety (ANSM) and on ClinicalTrials.gov (NCT05167331). Any protocol amendments will be justified, submitted to the scientific board, approved by the CPP, and recorded by the ANSM. Updates and modifications will also be logged on ClinicalTrials.gov. Informed consent will be obtained from each eligible child and their legal guardians following a detailed explanation of the trial by an investigator at the respective center. Patients and legal guardians will be informed of their right to withdraw from the study at any time and without explanation or consequences on the follow-up of the patient in the department. Regardless of withdrawal, patients will receive indicated dental treatment in their best interest, with documentation of the withdrawal process. Data confidentiality has been reviewed by the National Committee of Informatics and Freedom (Commission Nationale de l'Informatique et des Libertés (CNIL); reference methodology 001). The database does not contain the first and last names of enrolled patients.

There is no significance level in Bayesian analysis; however, credibility intervals will be calculated at 95% using the quantile method. The effect of a factor will be considered present if the probability that the effect is greater than the reference value is greater than 0.975 or less than 0.025. Non-inferiority can be concluded if the upper limit of the 95% credibility interval for the mean difference of Venham score between VR and EMONO is less than 0.1.

Dissemination of the results

The preparation of manuscripts reporting the results of this RCT will adhere to the Consolidated Standards of Reporting Trials (CONSORT) guidelines [27], and the outcomes will be published in international peer-reviewed journals. The authors of these publications will include individuals involved in developing the protocol, conducting the trial, and writing the manuscript and report. A summary of the study results will be available on ClinicalTrials.gov to ensure broad access to the findings. Data sharing will be conducted at the participant level, and access to the complete protocol can be provided upon request.

Adverse effects

Adverse effects, occurring in approximately 0.5–1.2% of patients after EMONO inhalation, mainly consist of nausea and vomiting. Other potential adverse effects may include oversedation, sweating, dysphoria, restlessness, panic, headache, dizziness, hallucinations, diffusion hypoxia, and expansion of gas-filled spaces. These effects are typically minor and reversible upon discontinuation of inhalation. They can arise during treatment and usually dissipate within minutes after discontinuing inhalation of the mixture [7, 8].

Regarding VR, some individuals (1/4000) may experience dizziness, eye strain, or muscle contractions in response to light stimulation or beams of light. These episodes are more common in children and young adults (Oculus Rift Health and Safety and Warranty Guide). Other signs of discomfort (eye fatigue, altered vision, disorientation, imbalance, coordination difficulties, anxiety attacks, headaches, nausea, vomiting) should prompt discontinuation of VR headset use. These symptoms of VR exposure typically resolve after ceasing headset use [15, 16].

Discussion

The conception of this protocol and the experimental design were based on the following main goals: to evaluate the efficacy and tolerance of a standardized and hypnosis-based VR device on anxious children undergoing dental treatment and to compare to the gold standard which is a pharmacological sedation using EMONO inhalation. Additionally, the secondary goal is to examine the clinical success of sedation considering various parameters as children's behavior or occurrence of adverse events, rather than solely focusing on the completion of dental treatment. It is also interesting to study whether child's temperament can impact the acceptance of virtual reality and the response of the child, the possibility of inducing this hypnotic state being also evaluated [19].

The VR device used in this study, HypnoVR®, combines hypnosis and passive distraction using virtual reality headsets to make the technique accessible to a wide range of patients. A combination of auditory and visual verbal guidance enables reproducible hypnosedation of the patient. Specifically, guided breathing sequences and heart coherence, along with specifically composed music based on recognized principles of music therapy, complement the device for a unique therapeutic multisensory immersion experience. The major advantage of this non-pharmacological approach lies primarily in the absence

of side effects, the quality of the "sedation" it provides, and the removal of external anxiogenic stimuli and dental environment for the child. The benefit of this device lies in passive distraction using virtual reality glasses and therapeutic hypnosis scenarios with audio, verbal, and visual guidance.

For the child, it involves:

- Immersing in a three-dimensional hypnotic environment
- Destigmatizing the dental office environment by providing a fun and familiar object
- Encouraging the child to return to the dental office for a normal follow-up without sedation
- Providing an additional alternative to general anesthesia for anxious children with contraindications to medication sedation

For the dentist, it involves:

- Facilitating dental care
- Reducing stress among practitioners
- Focusing on treatment while letting the child be an active participant in their hypnotic experience
- Conducting a reproducible and effective therapeutic hypnosis session without the need for hypnosis training

Upon conducting a search of the MEDLINE database for randomized clinical trial (RCT) on the use of virtual reality in dentistry, a variety of study designs have been identified. Many of these studies are randomized controlled trials, utilizing a parallel experimental design with two groups: one utilizing virtual reality headsets and the other serving as a control group without such headsets [22–24]. Additionally, a crossover clinical trial design has been observed, in which subjects are divided into two homogeneous groups and undergo two iterative dental intervention sessions [25]. In this design, the subjects in the first group receive virtual reality during the first session, while the subjects in the second group receive it during the second session. The crossover design allows for each patient to serve as their own control, providing a more reliable comparison than parallel-group studies by eliminating variability between subjects.

One of the challenges faced by the authors is the clinical protocol. Due to the nature of the virtual reality device, it appears difficult to compare it with other distraction methods or sedation or even a control group, in a single or double-blind fashion. This open-label protocol may introduce potential bias; therefore, it is essential to carefully analyze markers to ensure that follow-up and evaluation of outcome measures are carried out identically in both groups, which is often not clearly stated in studies [22]. The evaluator, the investigator, and the patient are all aware of the ongoing intervention, which brings obvious risks of detection bias. This explains the need to hide the child's face in the treatment videos. This approach ensures that the external evaluator remains unaware of whether the sedation method employed during the session (EMONO or VR) was used when evaluating the child's behavior. The downside of this method is the inability to evaluate the facial expression of the children. We proposed to focus on the Legs, Activity, Cry, and Consolability of the FLACC scale. Also, to enhance the intra-examiner reliability of the tools, a rigorous approach was adopted. This involved conducting video assessments twice by the same examiner, with a considerable time gap of at least 5 months between assessments. Additionally, after this interval, a second randomization of the videos was performed. By evaluating the same videos at two separate timepoints, several months apart, the potential for biases or inconsistencies in the examiner's judgment can be minimized. The extensive time gap between assessments lowers the likelihood of the examiner recalling specific details or impressions from the initial evaluation, ensuring a more unbiased evaluation during the second round. Additionally, the randomization of videos in the second round adds another layer of methodological rigor by presenting the videos in a different order than during the first assessment. This prevents the examiner from relying on memory or familiarity with the videos' sequence and ensures that each video is evaluated independently, without the influence of previous viewings. This systematic approach contributes to the reliability of assessment tools by reducing sources of bias and increasing consistency in the examiner's judgments over time.

Authors often prioritize objective criteria such as the measurement of salivary cortisol levels for the indicator of stress level in studies involving dental sedation [22, 23, 28–30]. While salivary cortisol is a non-invasive biomarker for stress, it is subject to various factors that can affect its measurement and potentially lead to inaccurate results. For instance, cortisol levels can fluctuate significantly throughout the day due to factors like circadian rhythms, food intake, and physical activity, which can complicate establishing a reliable baseline and interpreting findings accurately [31]. Cortisol levels may be influenced by various stressors beyond dental procedures, including environmental stressors, emotional factors, and other medical conditions, leading to difficulty in isolating the specific effects of dental sedation [32]. While providing one measure of stress, it may not capture the full spectrum

of physiological and psychological responses to dental sedation, such as heart rate variability, subjective anxiety levels, or behavioral indicators. Finally, salivary cortisol measurement requires specialized equipment and laboratory analysis, which can be costly and logistically challenging. That is why in our study, we chose child behavior hetero-evaluation as the primary outcome, aligning with the majority of RCTs in this field [18, 28, 29, 33]. It will be evaluated by the VMS as well as the FLACC standardized scales. The use of two scales instead of just one might help to reduce the risk of bias. Yet, we decided to include other more objective outcome criteria such as variations in vital physiological parameters during the session (pulse oximetry and heart rate). This approach aims to better translate our protocol's findings into improved clinical practice and a deeper understanding of conscious sedation prognosis and outcomes. The absence of a standardized behavior assessment scale for pediatric sedation trials is challenging for comparing different clinical studies. However, the VMS and FLACC scales appear as widely used and objectives scales in assessing behavior during pediatric dental sedation. Their widespread use could facilitate data pooling in a systematic review.

Only one investigator and one external examinator were appointed in this RCT. Limiting the involvement to only one investigator and one external examiner in a clinical trial offers several advantages in consistency throughout the trial. With fewer individuals involved in data collection and evaluation, there is a reduced chance of variability in assessments. It also helps maintain uniformity in the application of protocols and assessment criteria, minimizing potential biases or inconsistencies.

Based on continuous VMS evaluation, the sedation procedure is considered a failure if the VMS score is 3 or higher at two separated timepoints during the session. We feel the need to be clear on the threshold for success since it often varies between RCT and some do not even disclose the exact terms for success. Furthermore, we cannot deem a sedative regimen successful if it is associated with concerning adverse events, which need to be evaluated systematically.

Two recent meta-analyses, published in 2019 and 2020, have studied the effectiveness of virtual reality devices for children during dental procedures [33, 34]. The first concluded that children benefiting from audiovisual distraction show a lower heart rate during local dental anesthesia (mean difference equals −3.78; 95% CI, −6.73, −0.83; $p = 0.01$; I2 = 61%). This is based on 352 participants across 6 studies. However, there was no significant difference for blood oxygen saturation [33]. In contrast to the first meta-analysis, the second showed no significant improvement during local anesthetic administration (mean difference equals −0.41, 95% CI equals −0.91, 0.08) and placement of rubber dam (mean difference equals 0.17, 95% CI equals −0.33, 0.68). The authors evaluated nine studies to answer the question "Can we observe an improvement in a child's behavior, pain perception, or anxiety when virtual reality (VR) is used during dental treatment?" They concluded, however, that VR audiovisual distraction can significantly reduce pain perception and improve a child's behavior during cavity removal and restoration placement (mean difference equals −0.46, 95% CI equals −0.91, −0.01) (children who used VR glasses had a reduction of 0.70 in the average score of the FACES scale during dental restoration) [34].

These meta-analyses, despite following the data collection and analysis methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions, have limitations in interpreting their results. Firstly, the selected articles are not at a low risk of bias. As previously mentioned, due to the nature of the device, which delivers its action in an obvious and non-concealable manner, an open protocol seems inevitable. Additionally, heterogeneity among the studies in the literature complicates their comparison:

- Heterogeneity in participant characteristics and past dental experiences
- Heterogeneity in the type of dental intervention
- Diversity of virtual reality devices and entertainment programs offered
- Disparity in the chosen pain and anxiety scales, with hetero- or self-evaluations, making inter-study comparisons difficult
    - For pain (Visual Analog Scale, Wong Baker Faces Scale, Faces Pain Scale Revised)
    - For anxiety (Consolability Scale FLACC, Verbal Rating Scale, Modified Dental Anxiety Scale, Corah Anxiety Questionnaire, Venham Clinical Anxiety Rating Scale)

Furthermore, the studies found in the literature do not mention potential factors influencing patient acceptance and hypnotic susceptibility. According to Erickson's work on his "hypnotizability" scales, while 100% of patients can experience a hypnotic experience, only 25% of subjects are highly hypnotizable, 50% are minimally hypnotizable, and 25% are not hypnotizable at all [35]. It would also be interesting to study if the child's temperament can impact the acceptance of virtual reality and the possibility of inducing this hypnotic state in these patients [19].

A pilot study, with a similar protocol, conducted in our department in 2020 showed a significant reduction in anxiety (by 45%) during virtual reality sessions, with an

average patient satisfaction rating of 8/10. Good clinical feasibility of virtual reality was demonstrated, with the ability to perform oral surgery, endodontic procedures, or conservative treatment. Long clinical sessions (lasting more than 1 h) were also conducted under virtual reality, as part of complex dental rehabilitation for dental anomalies, with a good level of anxiety reduction.

In conclusion, this study protocol proposed an improved analysis of pediatric dental sedation, with the potential to impact both public and private healthcare services.

Trial status

This RCT began in June 2022 and the process of recruitment is ongoing.

Abbreviations

ASA	American Society of Anesthesiologists
EMONO	Equimolar Mixture of Oxygen and Nitrous Oxide
VR	Virtual reality
MVS	Modified Venham Scale
DBMP	Dental behavior management problems
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
FLACC	Face Legs Activity Cry Consolability
CONSORT	Consolidated Standards of Reporting Trials
EAS	Emotionality Activity Sociability
VAS	Visual Analog Scale
RCT	Randomized clinical trial

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

The role of authors and contributors was defined according to the International Committee of Medical Journal Editors. NMD, FC, MCM, and FL contributed to the overall conceptualization of the study and study design. NMD is the investigator and FC the external examinator. NMD drafted this manuscript. FC and MCM helped with the anxiety and pain assessment design and critically revised this manuscript. FL helped with the statistical plan and critically revised the manuscript. All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data availability

The datasets generated by the current study protocol will be available from the corresponding author on reasonable request.

Declarations

Competing interests

The authors declare that they have no competing interests.

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