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Review

Intranasal Dexmedetomidine as Sedative for Medical Imaging in Young Children: A Systematic Review to Provide a Roadmap for an Evidence-guided Clinical Protocol

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Abstract: There is an increasing need for effective anxiety and pain reduction during medical imaging procedures in children. This is a complex issue, addressed by both non-pharmacological or pharmacological approaches. Dexmedetomidine is a fairly recently marketed, selective α2-adrenergic agonist, and can be administered intranasally. To develop an evidence-guided clinical protocol, we investigated its (side)-effects, preconditions and safety aspects following intranasal dexmedetomidine in children (1 month-5 years) for procedural sedation during medical imaging. To do so, a systematic search (PubMed, Embase, CINAHL (12/2021)) was performed to identify clinical studies on intranasal dexmedetomidine for procedural sedation for medical imaging (Computer Tomography, Magnetic Resonance Imaging). Following screening and quality assessment, 8 studies were retained. Nasal nebulization was considered the best administration method, dosing varied between 2 to 4 µg/kg (age-dependent) 30-45 minutes prior to imaging, and contra-indications or restrictions on oral intake were somewhat consistent across studies. Valid sedation scores were routinely used to assess sedation and the need for rescue dosing, while discharge was generally based on the Aldrete score (score ≥9). Heart rate, blood pressure and saturation were routinely monitored, with commonly observed bradycardia or hypotension (decrease by 20%). Based on these findings, a roadmap for evidence-guided clinical protocol was generated.

Keywords: procedural sedation; children; dexmedetomidine; imaging

1. Introduction

The charter of United Nations Human Rights clearly states that all measures should be taken to prevent or relieve pain, physical discomfort and emotional tensions in children [1]. Anxiety and pain in children are both complex and multi-dimensional phenomena, as children are confronted with potential separation from their parents or loss of control during hospitalization. The unfamiliar environment and recall of previous experiences may further add to their stress and anxiety. More than half of all children who undergo a procedure in the hospital experienced prior intense anxiety [2,3]. The focus on maximum anxiety and pain reduction during an intervention in children was one of the drivers to create the PROSA-team (PROcedural Sedation and Analgesia) within University Hospitals Leuven, as recently described in this journal [4]. During interventions, such dedicated teams apply both non-pharmacological and pharmacological approaches. In addition to distraction and supportive therapy as non-pharmacological interventions, pharmacological

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interventions include fentanyl, midazolam, and more recently, also dexmedetomidine [4,5]. Specific during imaging procedures, avoiding uncontrolled behavior or movement artifacts is hereby of additional importance.

Dexmedetomidine is a selective α2-adrenoceptor agonist with sedative, anxiolytic, sympatholytic and analgesic sparing effects [6]. Dexmedetomidine also has dose-dependent hemodynamic side-effects. At lower exposure, central effects dominate, which leads to a decrease in heart rate and blood pressure. At higher exposure, peripheral vasoconstrictive effects predominate, resulting in an increase in systemic vascular resistance and blood pressure, while the bradycardia effect is further emphasized [7]. Dexmedetomidine is registered for sedation of adults admitted in an intensive care unit, while its off label use (*'no recommendation on a posology can be made')* becomes more common in children [7,8]. This is because of its perceived ability to result in adequate procedural sedation with a relatively low risk of respiratory depression, compared to benzodiazepines or opioids [9]. The minimal influence on respiration combined with the fact that the patient can be easily awakened, makes dexmedetomidine an interesting alternative in children [10]. However, its safety and efficacy in infants and children have not yet been formally established [7].

Given the emerging use in children, there is an need for indication-specific clinical protocols, reflecting the policies related to off-label use of medicines in children [11]. The most common indication for use in children is to facilitate radiological procedures. During such procedures, the child is expected to lie down without movement, as this can lead to artifacts and poor image quality. In addition, medical imaging can also induce anxiety in the child, related to e.g. noise or environment. We therefore aimed to investigate the (side)-effects, preconditions and safety aspects of intranasal dexmedetomidine, used as sedative for procedural sedation during medical imaging in children from 1 month to 5 years, with the aim to develop a roadmap for an evidence-guided protocol for clinical use. To do so, we conducted a systematic review on intranasal dexmedetomidine in children in the setting magnetic resonance imaging (MRI), computed tomography (CT) or nuclear medicine imaging. The study population was limited to children between 1 month and 5 years, as newborns likely have specific risk profile, while children over 5 years are already more commonly receptive for non-pharmacological interventions.

2. Materials and Methods

2.1. Selection Criteria and Systematic Search Strategy

We included studies of any type of design, in English, French or Dutch, published in the last decade. Study selection criteria were: 1) children from one month to five years of age, irrespective of comorbidities; 2) use of intranasal dexmedetomidine for procedural sedation during imaging (MRI, CT and nuclear medicine); 3) occurring in pediatric departments in hospitals, pediatric day care hospitals or radiology centers. We excluded studies where intranasal dexmedetomidine was administered to neonates and preterm infants, as well as studies in which there was an additional intervention occurred during medical imaging (like CT-guided puncture). The literature review was conducted in December 2021. Pubmed, Embase and CINAHL were consulted for study identification on dexmedetomidine use in children. To establish a search string, five main concepts were used.

1.Child, up to the age of five years

2.Procedural sedation

3.Dexmedetomidine

4.Intranasal administration

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5.Medical imaging

Index terms (MeSH, Emtree, Subject Heading) were added to each concept, as well as free text words and synonyms. Terms and words were interrelated using the Boolean term 'OR'. Examples of index terms that were used are: 'Child, preschool', 'Conscious sedation', 'Hypnotics and Sedatives', 'Nasal absorption' and 'Diagnostic imaging'. Free text words and synonyms such as 'Infant', 'Moderate Sedation', 'alpha 2 Adrenergic Receptor', 'Intranasal administration' and 'Radiologic and Imaging Nursing' were added. Finally, these five concepts were combined in one search string using the Boolean term 'AND'. In addition to this search string, we also applied the snowball method as references of studies that were retrieved were also verified. In addition, we were assisted by an expert who could also provide us with relevant publications.

2.2. Screening Process

After the studies were identified and duplicates were removed, two researchers (K.H., L.R.) individually reviewed all search results. Disagreements were discussed first, and if inconclusive, the decision was left to a third reviewer (K.A.). The first screening phase consisted of including studies based on title and abstract. Each researcher screened the studies individually and labeled them with '0' (not relevant) or '1' (possibly relevant). Articles labeled with '1' were taken to the next screening phase. The second phase involved the inclusion of studies based on its full text assessment. Again, score '0' was used for exclusion, '1' for inclusion.

2.3. Quality Assessment and Data Extraction

The next step in the process was to assess the quality, and subsequent extract all relevant information, related to the research question of the included articles. Quality assessment was based on standardized tools, related to the study design. The Jadad scale was used for randomized-controlled trials (RCT) [12], the Newcastle-Ottawa Scale (NOS) for nonrandomised studies [13], the National Institute of Health (NIH) Quality assessment tool for observational cohort and cross-sectional studies [14] and the AMSTAR-2 score for systematic reviews [15]. Extraction was structured by means of a data extraction tool. In this tool, data were collected for each study, namely: tile, author and year; study design and characteristics; sample and inclusion/exclusion criteria; setting and type of medical imaging; administration method, time and dose: assessment tools; possible side-effects; results. Articles were analyzed individually by both researchers and then combined in the data extraction tool, to facilitate comparison between studies.

3. Results

3.1. Selection Criteria and Systematic Search Strategy

The results of our search strategy are summarized in a PRISMA flow diagram (Figure 1). Most studies were retrieved in PubMed, while some additional studies were found by the snowball method, or were provided by an expert (K.A.). We identified 60 studies in total. Of these, seven duplicates were removed, as well as ten studies that did not meet predefined filters for language and publication date (automation tools). In the first screening phase, 23 studies were excluded (title-abstract screening) and eleven were dropped during the second phase (full text screening). Finally, one study failed on quality assessment (3.2.), so that eight studies (2012-2021) were retained for data extraction (Figure 1).

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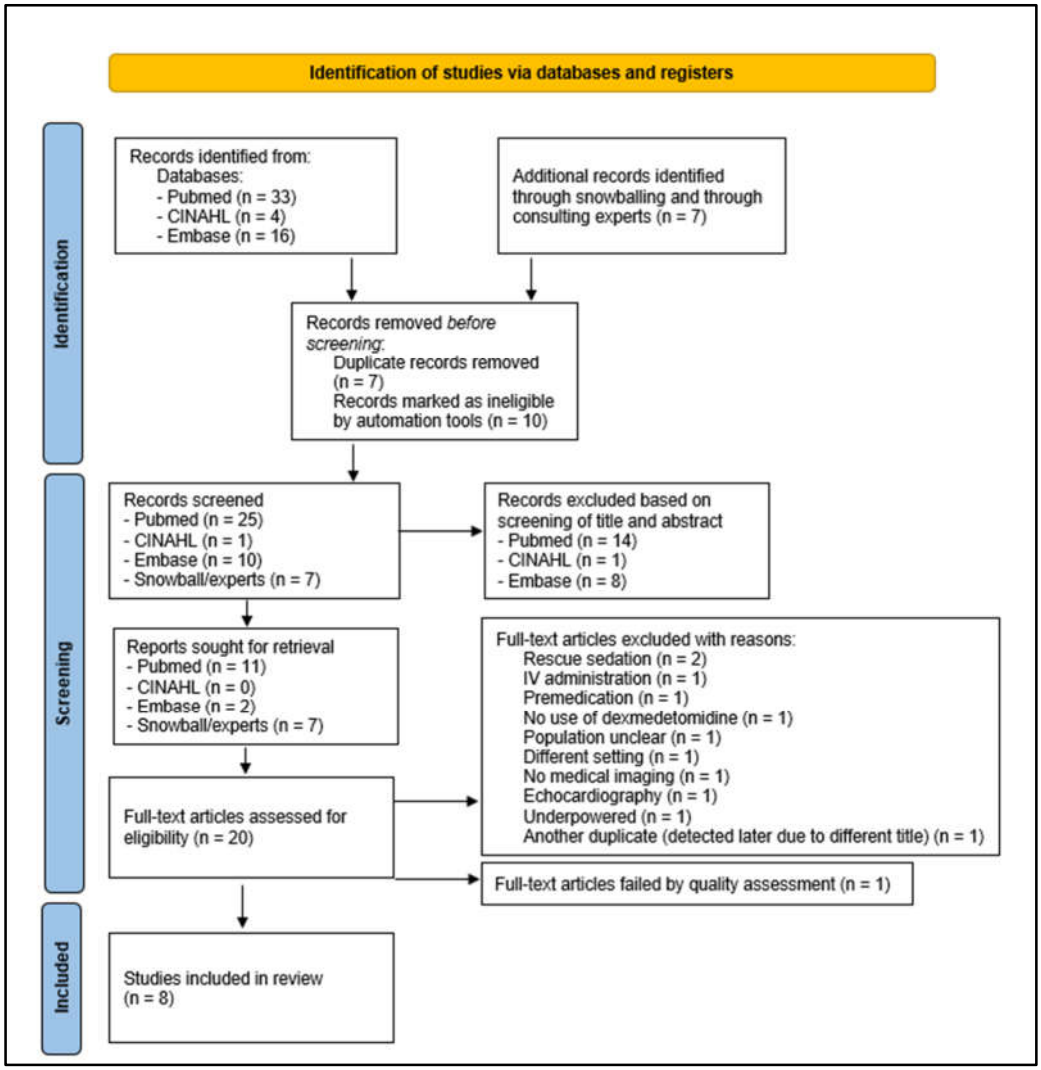

Figure 1. PRISMA 2020 flow diagram [16].

3.2. Quality Assessment

Nine studies retained after screening underwent quality assessment, with an assessment tool adapted to their study design. Three RCT's were assessed using the Jadad Scale (score 0-5, score <3 reflects insufficient reporting on methodological quality) (Supplemental Materials, Table S1). All assessed RCT's scored well on methodological quality and were retained for data extraction, with a score of 5/5 for 2 RCT's [12,17,18], or 4/5 (blinding methodology not sufficiently well described) [12,19]. One study was analyzed based on the NOS scale (eight items, related to 'selection', 'comparability' or 'outcome'). This effort resulted in 7 stars, reflecting good methodological quality (Supplemental Materials, Table S2) [13,20]. Four studies were evaluated using the 'NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies' (Supplemental Materials, Table S3) [14,21-24]. This tool provides a list of questions to reflect on key concepts of internal study validity. Although some items were not always reported, could not be determined or were not applicable, all studies achieved at least a score of eight. Finally, one systematic review was assessed using the 'AMSTAR 2 Checklist' (Supplemental Materials, Table S4) [15,25]. This scale aims to provide an overview on weaknesses within critical areas, and potential bias elements. With all assessors involved (K.H., L.R., K.A.), we concluded that this publication insufficiently reported on their methodological approach in 10/16 items. We therefore decided not to retain this paper, so that eight papers subsequently underwent data extraction.

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3.3. Data Extraction

A complete overview on all characteristics of the individual studies (purpose and outcomes, study design and characteristics, type of imaging and sample size, inclusion and exclusion criteria, administration method, timing and dose, and outcome variables, including assessment tools is provided in the data extraction tool (Supplemental Materials, Table S5).

3.3.1. Purpose of Studies and Outcomes

Four studies explored dexmedetomidine effectiveness as most commonly studied aspect. However, there were some differences in indications for which dexmedetomidine was administered (premedication to facilitate preparatory interventions like transfer, intravenous infusion, or sedation for medical imaging). Sometimes the focus was somewhat broader, like safety aspects, or recovery time. One study sought to determine intranasal dexmedetomidine effectiveness as sole premedication to perform a CT scan [17]. Another study evaluated the efficacy (sedation and imaging quality), safety (hemodynamics, saturation) and outcome (discharge) of intranasal dexmedetomidine for CT scanning [22]. Ambi et al. examined the efficacy (University of Michigan Sedation Scale, UMSS ≥2 to enable transfer and child-parent separation) of a specific dose (2 μg/kg) of intranasal dexmedetomidine for MRI [21]. Tug et al. explored the dose-response pattern, assessing the Ramsay Sedation Score (RSS), hemodynamics, saturation and respiratory rate, need for propofol rescue, recovery), following either 3 or 4 μg/kg intranasal dexmedetomidine [18]. Yuen et al. compared oral (50 mg/kg) chloral hydrate to intranasal (3 μg/kg) dexmedetomidine 30 minutes before CT imaging on sedation (UMSS), discharge criteria (Aldrete score) and tolerance (palatability, vomiting). An audit study described the use of both intranasal dexmedetomidine (2.5-3 μg/kg) and midazolam (0.29-0.39 mg/kg) for MRI sedation [24]. Similarly, Jackson et al. audited their outcome (imaging quality) of MRI sedation in three consecutive protocols [20]. In one of these, intranasal dexmedetomidine was used as sole sedative. This section was included in the systematic review. Finally, Uusalo focused on intranasal dexmedetomidine (2-3 μg/kg) pharmacokinetics and -dynamics (comfort-B score, vital signs) [23].

Primary outcomes were time to recovery after sedation [19], adequate sedation (RSS≥4, no need for rescue intravenous sedation)[Ghai], mean time until sedation [18], successful sedation (imaging quality)[20], response to child-parent separation [21], efficacy measures (number of doses, time to achieve sedation, time to meet discharge criteria) [22], major adverse events [24] or pharmacokinetics [23]. Besides sedation and discharge scores, secondary outcomes related to safety (hemodynamics, respiratory rate), tolerance (palatability, vomiting), imaging quality, need for additional dosing, or parental outcomes.

3.3.2. Study Design and Characteristics, Sample Size, Inclusion and Exclusion Criteria

Study designs included RCT's, prospective or observational studies/audits. Three of these were double-blinded, two were single-blinded, three other studies were observational, not blinded. Five studies were prospective, four retrospective as the audit of Jackson reported both retro- and prospective data. Finally, one non-randomized, 'open label' exploratory study was included.

Five studies were related to MRI procedures, 3 involved CT scan. We noticed a large variability in sample size (range 28-256) between the studies. The age category of included studies was mostly on target (1 month-5 years), with minor deviations to the higher age. Inclusion criteria between studies were rather consistent. For example, American Society of Anesthesiologists (ASA) status I/II, scheduled imaging, informed consent, and patient age were commonly mentioned, with additional study-specific elements (peripheral catheter access, language skills, or operator). On exclusion criteria, we noticed more differences across studies. The following exclusion criteria were commonly present: allergy to study drugs or other products used, history of cardiac dysfunction or respiratory

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problems, presence of Ear, Nose Throat (ENT) diseases, severe organ dysfunction, or chronic drug use, along with study-specific elements (previous administration of sedatives, risk of vomiting or aspiration, presence of reflux).

3.3.3. Method of Administration, Timing and Dose

Two options for intranasal dexmedetomidine administration were reported. A mucosal nebulizer/nose spray was used in four studies, instillation into the nostril, using a tuberculin syringe or similar in the other studies. Both Tug et al. and Ambi et al. stated that nebulizing is more effective (covers larger area, higher bioavailability) [18,21]. There was some variability in the time of administration to planned imaging, from 30 to 60 minutes. Four studies used a pre-procedure nothing per os (NPO) policy. There was some difference in the hours of solid and artificial feeding between studies. For liquids, there was more consistency (2 hours). The dose used within the studies ranges from 2 to 4 μg/kg. The lowest dose (2 μg/kg) was used by Ambi et al. [21]. Jackson et al. distinguished between <15 kg and ≥15 kg (2 and 4 μg/kg) [20]. Ghai et al. and Filho et al. used 2.5 μg/kg [17,22]. If the RSS was still too low (<3), a second dose (1 μg/kg) was administered [22]. Another study used different doses for different age categories, with on average, 2.7 μg/kg for the group 0-2 years, and 2.9 μg/kg in the 2-6 years group [23]. Yuen et al., Sulton et al. and Tug et al. used 3 μg/kg, be it within a RCT design compared to 4 μg/kg [18,19,24].

3.3.4. Outcome Variables

Several physiological parameters (oxygen saturation, heart rate, blood pressure, respiratory rate) were repeatedly or continuously measured. These parameters were commonly collected as safety markers. Only Filho et al. reported hypoxia in one patient [22]. In contrast, a decrease in heart rate is more common, up to 20% lower compared to usual or initial values. Related to blood pressure, a decrease reflecting hypotension is common (9 % and 10 % in the Filho et al. and Yuen et al. study), be it that a decrease > 20% is very rare (one case in the Filho et al. study) [19,22]. The most commonly used assessment tools to quantify the degree of sedation were the UMSS or RSS. Threshold values for top-up dosing hereby showed some variability. Other tools applied were the Bispectral Index Score (BIS monitor) or Comfort-B score. The Aldrete score was commonly applied to determine when a patient was fit for discharge (minimum score 9). Other outcome variables related to imaging quality, or focused on parental outcomes (Parental Separation Score, Parental Satisfaction Score).

4. Discussion

Studies on intranasal dexmedetomidine as sedative for medical imaging in young children were only retrieved for MRI and CT procedures, although we assume that we can extrapolate these findings to nuclear medicine imaging. Both MRI and CT are associated with various individual levels of anxiety due to separation, unfamiliar environment, or recall. The duration is commonly much longer for MRI procedures, and MRI imaging is also associated with significant more noise, and this may alter the level and duration of sedation needed to collect clinical meaningful images. A specific aspect of sedation for radiological procedures is that not all children require sedation. To determine individual patient needs remains a challenge, impartially reflected by age. Assessing individual capabilities and needs, and matching them to what is needed for a successful procedure is a skill [26]. Related to this, we predefined a subgroup (1 month-5 years) as priority, assuming that this subgroup commonly needs pharmacological sedation, despite the existence of non-pharmacological tools. This does not mean that these non-pharmacological tools are not valuable to be considered in this age category, can either reduce or even replace drug exposure, and holds the promise of improve self-esteem and -control of the child. Procedure specific tools are - among others - MRI mock-up scanners, video or virtual reality systems, or ear protection to distract and reduce stress in patients, or a vacuum matress [2,3,4,26].

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Intranasal dexmedetomidine dosing ranged between 2 to 4 μg/kg, without clear difference between both imaging modalities (CT: 2.5-3 μg/kg [17,19,22]; MRI 2-4 μg/kg [18,20,21,23,24]) despites the clinical rationale to discriminate between both procedures, or co-medications used [20,24], while Jackson used a weight-based (15 kg threshold) dose. When assessing all retained information, it seems that dose decisions for clinical protocol development in part depend on the level and type of efficacy/safety outcome (effective sedation, versus time to discharge and side-effects) variables targeted. A lower dose (2 μg/kg, MRI) resulted in no side-effects, but additional dosing in 40% of patients [21]. Along the same line, a 2.5 μg/kg dose (CT) also resulted in additional the necessity of additional dosing in 33% of patients [17]. Higher doses (3-4 μg/kg) are more effective when using the need for additional dosing as outcome [18], but likely will result in a somewhat prolonged time until return to normal activities (4.3 h) [19], be it that Tug could not document a difference in recovery time (Aldrete score) between the 3 and 4 μg/kg group [18].

Besides the 2-fold range in dosing, the literature is neither fully conclusive on the administration method of intranasal dexmedetomidine. The use of nebulization or instillation was divided proportionally. Two studies that opted for instillation mentioned in their discussion that nebulization is the better option. Nebulized particles cover a larger surface area compared to nasal instillation, resulting in better bioavailability [18,21]. Also the pharmacokinetic study used a nebulizing medical device [23]. The time of administration varied across studies, between 30 and 60 minutes before initiation of the imaging procedure.

Besides dose selection and type and timing of administration, there are also some 'circumstantial' and 'procedural' aspects. Circumstantially, one may consider to apply a NPO policy. Each study prohibited clear liquids two hours before the procedure, but with less uniformity on milk feeling, and more diversity on limits for solid foods. Procedural practices relate to sedation and recovery assessment, monitoring, and exclusion criteria. To explore the sedation level, various measuring tools were used. The RSS was applied in four studies, be it with different thresholds, and higher for MRI than for CT (RSS of ≥4 or ≥5 for MRI [18,20]; ≥3 or ≥4 for CT [17,22]. The (modified) Aldrete (threshold 9) was most commonly used to assess recovery. In the majority of studies, physiological parameters were monitored before and after dexmedetomidine administration, with diversity in time intervals at which parameters were collected. Continuous monitoring of heart rate, blood pressure and oxygen saturation was commonly applied. Vomiting was an adverse event of special interest. Exclusion criteria related to drug allergy, ASA status III/IV and hepatic abnormalities. In addition, patients with cardiac abnormalities, central nervous system dysfunction, respiratory and renal dysfunction, mental retardation, or a risk of difficult intubation (ENT) are sometimes excluded from clinical studies.

A systematic review has strenghts, but obviously also has some shortages. First, one should realize that statistical significant findings retrieved in this systematic review, differ on their clinical relevance when considered for clinical protocol development. To illustrate this, a 2.8 minute difference between dexmedetomidine to chloral hydrate in time to sedation was statistically significant, but is not of clinical relevance [19], while adequate sedation or successful imaging [17,20,24], parental separation distress [18] or palatibility aspects [19] are more relevant outcome variables. Second, we were not always able to extract the data specific to our predefined age category, specifically for the higer age range. We have tried to address this by sending e-mails to the corresponding authors. As we have not received any response, we focussed on the mean or median age of the cohorts. Finally, our search strategy yielded only 60 results, this may be due to a narrow search string, or the fact that the medicine in fairly recently introduced in pediatric procedural sedation. Besides that, the ratio between articles out of a database and articles received from an expert is somewhat imbalanced. Considering these limitations, and based on the outcome of the systematic review, a roadmap as suggestion to develop an evidence-guided clincial protocol on intranasal dexmedetomidine in young children was generated (Table 1).

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Table 1. A suggested roadmap on aspects to consider to develop an evidence-guided clinical protocol on intranasal dexmedetomidine in young children .

aspects	suggestions	
contraindications	ASA-status III/IV; Hepatic abnormalities; Cardiac abnormalities; Central nervous system dysfunction; Respiratory or renal dysfunction; Risk of difficult intubation; Drug allergy	
dose	Age-related suggestion: 2,5 μg/kg under 1 year, 3 μg/kg in 1 to 3 years , 4 μg/kg in 3 to 5 years Modality-related suggestion: CT: 2.5-3 μg/kg; MRI 2-4 μg/kg	
administration method	Nebulization by mucosal spray	
timing of administration	30-45 minutes before the procedure	
NPO policy	Variability in practices - Clear liquids from one or two hours before sedation/procedure - Milk food from four to six hours before sedation/procedure - Solid food from eight hours before sedation/procedure In case of an urgency: consider specific guidelines, like American College of Emergency Physicians.	
sedation monitoring	A sedation scale should be used. Consider the use of the Ramsay Sedation Score (RSS) 10 and 20 minutes after administration To obtain adequate sedation, this score should be as follows: For MRI → ≥ 4 of ≥ 5; For CT → ≥ 3 of ≥ 4	
rescue medication	Several options: (1) additional dose dexmedetomidine, or (2) intravenous bolus propofol, or thiopental, or (3) intravenous/intranasal midazolam	
discharge	Modified) Aldrete score has to be registered after the procedure → threshold score ≥9, for discharge.	
monitoring	Continuous monitoring of heart rate and oxygen saturation is highly recommended throughout the procedure. If an abnormal heart rate is observed, blood pressure should also be measured*. *Blood pressure is not measured by default as it can result in arousal, and is a late indicator of circulatory failure.	
potential side-effects	Commonly occurring	Bradycardia with a decrease of < 20% Hypotension with a decrease of < 20%
	Less common occurring	Bradycardia with a decrease of > 20% Hypotension with a decrease of > 20% Vomiting
	Rarely occurring	Desaturation; Hypertension; Tachycardia
Non-pharmacological interventions	Suggest to consider simultaneous use of non-pharmacological interventions like hearing protection, matress, distraction or mock-up	

Supplementary Materials: Table S1: Overview assessments Jadad Scale, Table S2: Overview assessment Newcastle-Ottawa Scale, Table S3: Overview assessments National Institute of Health (NIH) Quality Assessment Tool, Table S4: Overview assessment AMSTAR 2, Table S5: Data extraction of the eight studies retained in the systematic review, reporting on purpose and outcomes, study design and characteristics, type of imaging and sample size, inclusion and exclusion criteria, administration method, timing and dose, and outcome variables, including assessment tools.

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