



## Original contribution

# The sedative effects of the intranasal administration of dexmedetomidine in children undergoing surgeries compared to other sedation methods: A systematic review and meta-analysis



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## ABSTRACT

**Study objective:** Administration of intranasal dexmedetomidine for sedation is comfortable and effective in children who are afraid of needles, and it offers efficient sedation similar to that of intravenous administration. We performed a systematic review and meta-analysis to evaluate the clinical effects of the pre-procedural administration of intranasal dexmedetomidine.

**Design:** We identified randomized controlled trials (RCTs) that compared intranasal dexmedetomidine administration to other administration methods of various sedatives or placebo from MEDLINE, EMBASE, Cochrane, KoreaMed and hand searches of trial registries.

**Setting:** Pediatrics who underwent interventional procedures and surgeries.

**Patients:** Children under the age of 18.

**Interventions:** Studies were included if they were compatible with the criteria that dexmedetomidine was administered intranasally.

**Measurements:** We pooled data on the sedation status as the primary outcome and considered the behavioral score, blood pressure, heart rate and side effects to be secondary outcomes. Risk ratio (RR) and the standardized mean difference (SMD) with 95% confidence intervals (CIs) were calculated for dichotomous and continuous outcomes, respectively.

**Main results:** This meta-analysis included 11 RCTs. The SMD for the sedative effects of intranasal dexmedetomidine was  $-2.45$  (random, 95% CI:  $-3.33, -1.58$ ) for continuous outcomes and RR of unsatisfactory patient outcome was  $0.42$  (M-H, random 95% CI:  $0.26, 0.68$   $I^2 = 45\%$ ) for dichotomous outcomes compared to that of intranasal saline. The SMD for the sedative effects of intranasal dexmedetomidine was  $-0.41$  (random, 95% CI:  $-1.09, 0.27$   $I^2 = 69\%$ ) for continuous outcomes and RR was  $0.43$  (M-H, random 95% CI:  $0.32, 0.58$   $I^2 = 0\%$ ) for dichotomous outcomes compared to that of per os benzodiazepines.

**Conclusions:** This review suggests that intranasal dexmedetomidine is associated with better sedative effects than oral benzodiazepines without producing respiratory depression, but it had a significantly delayed onset of effects.

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## 1. Introduction

Dexmedetomidine, a highly selective  $\alpha_2$ -adrenergic receptor agonist, has been used not only as a local anesthetic adjuvant for neuraxial and peripheral nerve blockage but also as an intravenous and intramuscular sedative with little depressant effect on the respiratory system [1–3]. After establishing the comfort and efficacy of

intranasal dexmedetomidine, the usefulness of the intranasal route was increasingly reported, especially in children with difficult intravenous cannulation and who are afraid to be separated from their parents [4]. However, the effectiveness of the intranasal route compared with other routes of administration has not been completely evaluated. The absolute bioavailability of intranasal dexmedetomidine administration was reported to be approximately 65% (35–93%) (median and range), and the peak plasma concentration of intranasal dexmedetomidine was reached in 38 min (15–60 min) [5,6].

We compared the sedative and clinical effects of intranasal dexmedetomidine with other sedative drugs and saline administered by various routes, including the oral, buccal, and intranasal routes,

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using a randomized controlled trial. We hypothesized that intranasal dexmedetomidine would be more effective for sedation without respiratory depression when compared to alternative conventional methods.

## 2. Materials and methods

We carried out a systematic review to find literature that compared the sedative effects of intranasal dexmedetomidine with a placebo or an alternative sedative agent, such as benzodiazepines, ketamine, and opioids. This systematic review was based on the Cochrane Review Methods and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [7].

### 2.1. Data & literature sources

We searched MEDLINE (January 1, 1976 to Dec. 31, 2014), EMBASE (January 1, 1985 to Dec. 31, 2014), the Cochrane Library of Controlled Trials (January 1, 1987 to Dec. 31, 2014) and KoreaMed (June 1, 1958 to Dec. 31, 2014) using the following search strategy: “Dexmedetomidine” or “Precedex” or “Adrenergic alpha-2 Receptor Agonists” or “Adrenergic alpha 2 Agonists” or “Adrenergic alpha-Agonists” or “Adrenergic alpha 2 Receptor Agonists”. We also searched with the keywords: preanesthetic or premedication or intranasal or nasal “Pre-anesthetic Medication” or “Premedication” or “Administration, Intranasal” or “Nasal Sprays”. Groups or trial or randomly or drug therapy or placebo or randomized or controlled clinical trial or randomized controlled trial not animals not humans and animals, was also searched. Search strategies were developed for each database, and the detailed search strategies are presented in Supplementary file S1 (S1 Appendix). After the initial electronic search, we additionally hand searched reference lists of retrieved studies and pertinent reviews for relevant articles. For unpublished and ongoing studies, we searched the international standards randomized controlled trial number registry (ISRCTN; isrctn.org) and the ClinicalTrial.gov registry. There were no other restrictions.

### 2.2. Study selection

Two reviewers (WJ Shin and JH Oh) decided to select studies according to the pre-specified selection criteria. We assessed the titles and abstracts of the identified studies. If the eligibility of a study was difficult to judge, the full article was assessed. Studies were included in our meta-analysis if they were compatible with the following criteria:

- (1) dexmedetomidine administered intranasally (intervention group)
- (2) benzodiazepine (mainly midazolam), opioids, ketamine or placebo (control group) administered via other routes including per oral, buccal and intranasal routes
- (3) only randomized controlled trials
- (4) no language restriction
- (5) children under the age of 18.

### 2.3. Data extraction

Two reviewers blindly performed data extraction using a predefined data extraction form. Any discrepancy unresolved by discussion was put under the examination of a third reviewer.

### 2.4. Assessment of methodological quality

Two reviewers independently assessed the methodological qualities for each study using Cochrane Collaboration's tool for assessing the risk of bias. Each risk of bias item is presented as a percentage across all included studies. Any unresolved disagreements between reviewers were resolved through discussion or by evaluation by a third reviewer.

### 2.5. Statistical analysis

The main outcome of this review was the effect of intranasal dexmedetomidine on sedation status (observed sedation score) as the primary outcome. For the secondary outcome, behavior scores, systolic blood pressure, and heart rate were determined. Both outcomes consisted of continuous and binary data. For sedation and behavior scores in continuous variables, we estimated weighted mean differences using the means and standard deviations from each study. For binary scores presented as satisfactory/unsatisfactory, we used the Mantel-Haenszel method to calculate risk ratios using the number of events in the control and intervention groups of each study.

First, we conducted a comparison of the sedation status between intranasal dexmedetomidine and intranasal saline groups. Then, we compared intranasal dexmedetomidine with the buccal dexmedetomidine groups. Third, we compared intranasal dexmedetomidine with the intranasal benzodiazepine, ketamine and fentanyl groups. Finally, we compared intranasal dexmedetomidine with per os benzodiazepine mixed with coke and orange juice, the use of which is widely accepted in pediatric interventional procedures and surgeries.

Heterogeneity was estimated by calculating the  $I^2$  statistic, which assesses the proportion of true difference (not random-error) within between-study inconsistencies.  $I^2$  values above 50% were considered to be moderately heterogeneous, and random-effect models were used for such studies or studies with clinical heterogeneity. We performed subgroup analyses of the administered drugs. We could not assess publication bias in these trials. Although 11 studies were included in this meta-analysis, each group contained fewer than 10 studies when sorted by comparison groups. Thus, we could not perform tests for funnel plot asymmetry because these tests are unable to effectively differentiate chance from asymmetry unless 10 or more studies are included. We used RevMan version 5.2 for all analyses.

## 3. Results

### 3.1. Identification of studies

Searches of the databases resulted in 1416 articles. Of these, 1142 publications were excluded, as it was clear from the title and abstract that they did not fulfill the selection criteria. For the remaining 23 articles, we identified 11 potentially relevant studies after scrutinizing the full manuscripts. Therefore, the total number of studies included in this review was 11 (Fig. 1). The following variables were extracted from the studies for the primary outcome:

- (1) Continuous data: mean and standard deviation of the sedative score of 343 participants from 4 studies.
- (2) Dichotomous data: the number of the participants who were not satisfied with intranasal dexmedetomidine in the 930 participants from 9 studies.

### 3.2. Description of the studies

The main characteristics of the study, such as nationality, year published, presence of funding, study design, population characteristics, and the study are described in Table 1. All of the studies except for one [8] were published in English.

Four randomized controlled trials (36.4%) included 262 participants and investigated the efficacies and side effects associated with intranasal dexmedetomidine pretreatments compared with those of intranasal saline (Table 2) [1 study [9] with continuous data and 3 studies [10–12] with binary data]. The effect size of buccal dexmedetomidine (continuous data) [13] was compared to that of intranasal dexmedetomidine. The effect size of intranasal benzodiazepine (continuous and binary data), [14] fentanyl (binary data), [11] and the dissociative anesthetic

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