REVIEW ARTICLE

Use of dexmedetomidine in the management of non-invasive mechanical ventilation in pediatric patients

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ABSTRACT

Introduction: Non-invasive ventilation is widely used in pediatric patients due to its effectiveness in treating respiratory failure; however, there is a high failure rate due to patient agitation. In this context, dexmedetomidine has been employed as a primary sedative agent or during the peri-extubation period.

Objective: To conduct a scoping review of observational studies in pediatric patients (0 to 18 years old) who underwent non-invasive mechanical ventilation with the use of dexmedetomidine.

Methods:Articles were retrieved from the databases PubMed/MedLine, EBSCO, EMBASE, Scielo, SCOPUS, Cochrane Library, Google Scholar, ScienceDirect, and journals available on the Portal de Periódicos of the Coordination for the Improvement of Higher Education Personnel (Capes). There was no limitation

regarding the period or year of publication, in order to critically analyze the main elements related to the interaction between dexmedetomidine, the pediatric population, and the use of non-invasive mechanical ventilation.

Results: The use of dexmedetomidine in pediatric patients undergoing non-invasive ventilation was considered positive after extubation, as it does not cause ventilatory system depression and has shown significant efficacy in patients who experienced agitation during non-invasive ventilation. However, its use during non-invasive ventilation was associated with hemodynamic adverse effects, such as bradycardia and hypertension, in addition to withdrawal symptoms reported after drug discontinuation.

Conclusion: The results of observational studies indicated that dexmedetomidine had a positive impact on pediatric patients undergoing non-invasive ventilation after extubation, although adverse effects such as bradycardia and hypertension may occur.

Keywords: Dexmedetomidine, Non-invasive ventilation, Child, Pediatric intensive care unit.

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Introduction

Non-invasive ventilation (NIV) is widely used in pediatric patients in intensive care units and has proven effective in treating respiratory failure related to respiratory diseases. However, a high failure rate is often observed due to patient restlessness, leading to intolerance, which presents a clinical challenge. Consequently, there have been reports on the use of minimal sedation to improve tolerance to NIV, with dexmedetomidine (DEX) being one such sedative option[1,2].

Sedatives like dexmedetomidine provide effective sedation with a reduced risk of respiratory center depression and do not compromise airway patency1. DEX is an α2-adrenergic agonist that induces sedation and anxiolysis through receptors in the locus coeruleus, while its analgesic effects are mediated through spinal cord receptors. It also attenuates the stress response without causing significant respiratory depression[1,3]. Additionally, a reduction in weaning time has been observed with its use[1,4].

When used as a primary sedative or during the peri-extubation period, DEX has demonstrated superior sedation outcomes compared to other sedatives. It is well-tolerated with acceptable cardiovascular effects, provided bolus doses are avoided[1,5,6.] The most commonly reported adverse effects are hypotension and bradycardia, although these effects have been inconsistently reported in critically ill children [1,3,6].

Previous studies in the literature on the use of DEX in non-invasive ventilation in pediatric patients are still scarce, and more research is needed, since the use of DEX as a sedative is of paramount importance in association with NIV, as it presents a high failure rate due to restlessness in children when used without association with sedatives. Therefore, more research is essential to address the effectiveness and adverse effects of DEX[4]. Therefore, the objective of this work was to evaluate, through a scoping review, the use of dexmedetomidine in the management of non-invasive mechanical ventilation in pediatric patients.

METHODS

A systematic review of the literature was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, which include a checklist of 27 items and a four-phase flowchart. No restrictions were placed on the publication period to allow a comprehensive analysis of the key elements related to the interaction between dexmedetomidine, the pediatric population, and the use of non-invasive mechanical ventilation. The databases analyzed included PubMed/MedLine, EBSCO, EMBASE, SciELO, SCOPUS, Cochrane Library, Google Scholar, and ScienceDirect, as well as journals available on the Journal Portal of the Coordination for the Improvement of Higher Education Personnel (Capes). This review is registered with PROSPERO under number CRD42021265231.

The methodological quality of the included studies was assessed using the Newcastle-Ottawa scale, which evaluates the quality of observational studies based on three broad perspectives: selection of study groups, comparability of groups, and ascertainment of exposure or outcome for case-control or cohort studies, respectively.

The quality assessment was conducted independently by two fourth-year medical students, using the Newcastle-Ottawa scale to evaluate the risk of bias (Figure 2).

The cohort and case-control studies included in this review were scored based on three components: selection of the studied groups (0–4 points), comparability (0–1 point), and assessment of the outcome (0–3 points). The maximum score is 9 points, indicating high quality. The studies selected for this review had average quality, with scores ranging from 4 to 6 points.

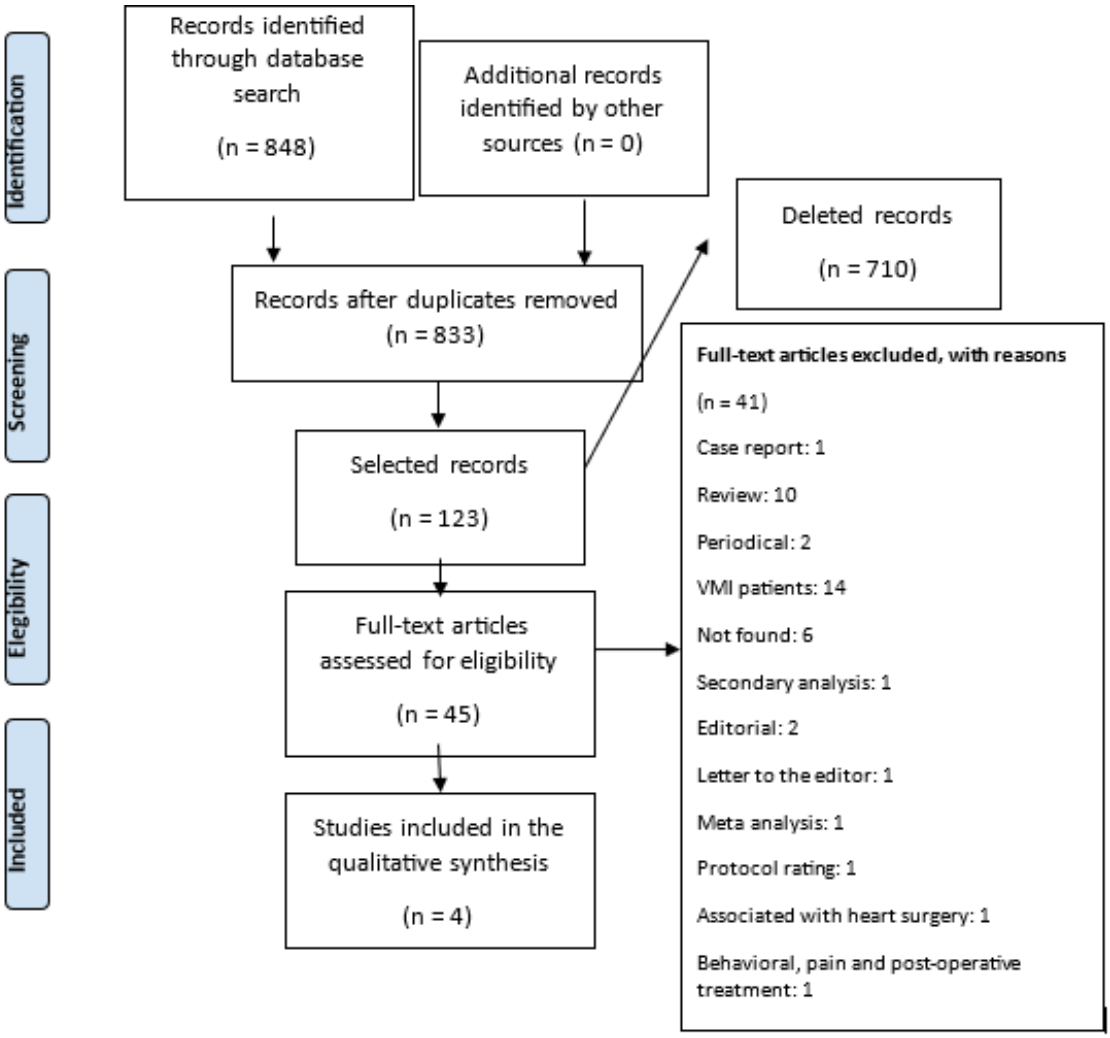
The MeSH terms were consulted and combined as follows: a) Non-invasive mechanical ventilation (Noninvasive Ventilations; Ventilation, Noninvasive; Ventilations, Noninvasive; Non-Invasive Ventilation; Non-Invasive Ventilations; Ventilation, Non-Invasive; Ventilations, Non-Invasive; Non Invasive Ventilation; Non Invasive Ventilations; Ventilation, Non Invasive; Ventilations, Non Invasive; Continuous Positive Airway Pressure; Intermittent Positive-Pressure Breathing; Intermittent Positive-Pressure Ventilation). b) Precedex (MPV-1440; MPV 1440; MPV1440; Precedex; Dexmedetomidine Hydrochloride; Hydrochloride, Dexmedetomidine; Dexmedetomidine; DEXDOR). c) Pediatrics (Children; Preschool Child; Children, Preschool; Preschool Children; Infant; Infants, Newborn; Newborn Infant; Newborn Infants; Newborns; Newborn; Neonate; Neonates). Equivalent terms in Portuguese were used to search for national journals in the Scientific Electronic Library Online (SciELO) and Google Scholar.

The eligibility criteria are presented in the following table:

Population	Pediatric from 0-18 years
Concept	Use of DEX on NIV
Context	Pediatric ICU
Types of studies	All

Results

A total of 848 studies were initially selected based on the pre-established inclusion criteria, as illustrated in the flowchart (Figure 1). After screening by title, 124 studies progressed to the next stage, where the abstracts were reviewed. Ultimately, 46 articles were selected for full-text reading, and 4 studies were included in this review. These articles were classified based on the main author, publication date, objectives, study type, participant population, type of analysis, main results, and outcomes.



NOS	Seleção				Comparabilidade	Resultados			Total
Autor (ano)	1	2	3	4	5	6	7	8	pontos
Brittany L. Shutes, MD1/ 2018	-	-	★	-	★	★	★	★	5
Rasika Venkatraman, MD1/ 2017	-	-	★	★	★	★	★	★	6
M. Piastra/ 2018	-	-	-	★	★	★	★	★	5
Heidi L. Banasch/ 2017	★	★	-	-	★	-	★	-	4

Figure 2- Classification table of articles, risk of bias for cohort and case-control studies using the Newcastle-Ottawa scale.

None of the studies were excluded from this review by consensus of all research participants. Assessing the quality of studies using the Newcastle-Ottawa scale, a low risk of bias was identified for this type of study design.

After the selection process, 4 retrospective cohort studies were included in this work, one of which was published in 2017 and three in 2018 and the study sample composed of pediatric patients aged zero to 18 years (table 1). The outcomes and variables analyzed were: possible hemodynamic effects, presence of abstinence upon drug withdrawal, tolerability, control of agitation and level of sedation during the use of non-invasive mechanical ventilation.

The selected articles are then presented in Table1.

Author, year	Types of studies	Sample	Outcome	Resultado/Conclusão
Shutes, Brittany L; 2018	Restrospective study	n=382 (<18 years)	Evaluate hemodynamic effects during the use of NIV.	The use of DEX for non-invasive positive pressure ventilatory sedation in pediatric intensive care has predictable hemodynamic effects including bradycardia and hypotension. 19% of the sample showed signs of withdrawal after withdrawing from the drug.
Banasch HL; 2018	retrospective cohort study	n=219 (<18 years)	Tolerability of dexmedetomidine and abstinence from drug withdrawal during NIV use.	Adverse effects appeared more common in younger patients and those with prolonged infusions. Signs of withdrawal were observed in 80% of the sample. The authors suggest that the use of DEX in patients under NIV has a positive effect after extubation as it does not depress the ventilatory system. Controlled studies are needed to better understand the optimal use of DEX as it relates to the prevention and treatment of adverse effects and withdrawal, and especially for use in non-OTI patients.
Piastra M; 2018	retrospective cohort study	n=40 (16 months)	Control of agitation and NIV intolerance	Four patients who failed NIV, all due to worsening pulmonary condition, required OTI and MV. 36 patients were successfully weaned from NIV under DEX sedation and discharged from the PICU. Data suggest that DEX may represent an effective sedative agent in infants and children who experience agitation during NIV. Early use of DEX in infants/children receiving NIV for AKI should be considered safe and capable of improving NIV, thus allowing lung recruitment and patient-ventilator synchronization.
Venkatraman R; 2017	cohort study	n=202 (0 - 2 years)	Level of sedation and hemodynamic effects during use of VNI	Success when used to wean from NIV to nasal cannula or room air. DEX was often effective as a continuous sedative infusion during pediatric NIV. Cardiorespiratory events associated with its use were typically mild and/or reversible with dose reduction, fluid administration and/or non-invasive ventilation titration.

Caption: DEX (dexmedetomidine); IOT (orotracheal intubation); ARF (acute respiratory failure); PICU (Pediatric Intensive Care Unit); MV (mechanical ventilation); NIV (non-invasive ventilation

Based on the retrospective cohort studies included in this review, the dosages of dexmedetomidine administered to patients undergoing non-invasive ventilation (NIV) were summarized and detailed in Table 2. The maximum doses varied across the studies, ranging from 0.61 µg to 1.4 µg. Following administration of the maximum dose, a decrease in heart rate predominated, often leading to bradycardia, while an increase in systolic blood pressure, leading to hypertension, was also commonly observed. Additionally, a minority of cases experienced hypotension.

Table 2 - Dexmedetomidine Dosages in Included Studies

Author, years	Sample	Dosage
Shutes, Brittany L; 2018	n=382 (<18 years)	1 µg / kg / h (0,6-1,2 µg / kg / h)
Banasch HL; 2018	n=219 (<18 years)	0,7 µg / kg / h
Piastra M; 2018	n=40 (16 mouths)	1,4 µg / kg / h
Venkatraman R; 2017	n=202 (0 to 2 years)	0,61 µg / kg / h (variação, 0,4-0,8 µg / kg / h)

DISCUSSION

Currently, several drugs are used to promote sedation and analgesia in patients admitted to intensive care units. These drugs, including barbiturates, opioids, benzodiazepines, and others, are administered alone or in combination to achieve these goals. However, it is observed that these drugs often fail to reach an optimal balance between sedation and analgesia. Additionally, many of these drugs present significant and potentially harmful adverse effects, which limit their use.

Sedating children for outpatient procedures is particularly challenging. Ideal sedation should provide a rapid and reliable onset of effects while maintaining patent airways, ensuring adequate spontaneous ventilation, preserving cardiovascular stability, and allowing for a smooth and predictable awakening. Therefore, dexmedetomidine, an alpha-2 receptor agonist, has been favored for sedation, especially in pediatric patients, due to its absence of respiratory depressant effects, adequate sedative and analgesic action, and favorable antiarrhythmic properties.

Dexmedetomidine (DEX) exerts various effects on different systems: it has sedative and anxiolytic properties, plays a crucial role in modulating pain (reducing the need for other anesthetics), inhibits norepinephrine exocytosis (causing systemic arterial hypotension and bradycardia), does not induce significant respiratory depression, and has antisialogogue effects, among others. DEX also causes xerostomia and nausea, directly inhibits insulin release by pancreatic cells without causing hyperglycemia, and can inhibit antidiuretic hormone release, increasing glomerular filtration rate.

DEX is considered a safe drug for adult intubation due to its lower likelihood of causing respiratory depression, delirium, and tremors compared to similar drugs like benzodiazepines. However, abrupt discontinuation of DEX, similar to clonidine and other alpha-2 adrenergic drugs, may lead to withdrawal symptoms, including agitation, headache, increased blood pressure, and elevated circulating catecholamine levels, which are among the signs and symptoms of withdrawal .

The use of DEX in patients undergoing non-invasive ventilation (NIV) has been positive, as it does not cause ventilatory depression and is particularly effective in pediatric patients who experience agitation during NIV. However, the use of DEX as a sedative in NIV has been associated with hemodynamic adverse effects, such as bradycardia and hypertension, and withdrawal symptoms have been reported upon discontinuation. These adverse effects are commonly observed in pediatric patients and in those using DEX for extended periods.

High bolus doses of DEX may result in an initial response of bradycardia and hypertension, caused by the peripheral stimulation of alpha-2b receptors, followed by central sympathectomy and a subsequent decrease in blood pressure. However, DEX does not depress the cardiovascular system. Conversely, a high risk of bradycardia has been reported when DEX is administered in combination with sympatholytic or cholinergic agents, especially in the presence of concomitant vagal stimulation .

Studies have indicated that plasma levels of 0.5 to 1.2 ng/mL are ideal for maintaining sedation with beneficial pharmacodynamics. High doses (8.0 ng/mL) have been associated with alpha-2C agonist-induced peripheral vasoconstriction, increased systemic vascular resistance, and a lower cardiac index due to catecholamine suppression and deep sedation, without causing clinically significant respiratory depression .

Dexmedetomidine can induce amnesia in a dose-dependent manner and cause anxiety and sedation. Its main advantage is sedation with minimal effects on ventilation .

Recently, a double-blind, randomized controlled clinical trial by Shi et al. evaluated behavioral changes after postoperative tonsillectomy without adenoidectomy in 90 patients aged 2 to 7 years who received a single dose of 0.5 μg/kg DEX along with sevoflurane anesthesia. The primary outcome was the incidence of delirium within 30 minutes after extubation. Secondary outcomes included pain incidence, time to extubation, length of stay in the post-anesthesia care unit, adverse events, and the incidence of negative postoperative behavioral changes. The authors found that dexmedetomidine reduced the incidence of delirium (P = 0.033) and pain (P = 0.006) but prolonged the time to extubation (P = 0.001). These findings align with those of Guler et al. and Shukry et al., who demonstrated that dexmedetomidine at dosages of 0.5 μg/kg 5 minutes before the end of surgery and 0.2 μg/kg/h during surgery, respectively, reduced the incidence of delirium in patients requiring sevoflurane anesthesia[19,20,21].

CONCLUSION

Based on the results discussed in the studies mentioned above, dexmede-

tomidine (DEX) demonstrated positive outcomes in patients undergoing non-invasive ventilation (NIV). However, despite the generally good tolerance to DEX, adverse effects such as bradycardia and hypertension were reported following withdrawal of the medication. Moreover, there are few studies that specifically explore the use of DEX in pediatric patients receiving NIV, and the available studies are primarily observational. Therefore, future research is needed to better elucidate the use of DEX and its effects, as it is a significant ally in non-invasive ventilation. Further studies are crucial, especially considering that NIV may have a higher failure rate if the patient is intolerant to pressure therapy.

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