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Dexmedetomidine – a new option for sedation of patients on the autistic spectrum?

Dexmedetomidina – uma nova opção para sedação de pacientes do espectro autista ?

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Abstract

Introduction: *Dexmedetomidine is considered a promising medication used for sedation in the most varied areas of health. Considered a central α-2 agonist, its use is safe thanks to the presence of minimal respiratory depression.* ***Objective****: This study aims to perform a literature review on the effects of sedation with the use of Dexmedetomidine in patients with autism spectrum disorder.* ***Methods****: For a proper analysis, a review strategy was developed of literature in the databases Pubmed (MEDLINE), Scielo, Cochrane and Google Scholar. English articles published between 2008 and 2019 were included. Results: 9 articles were selected, which include case reports, prospective and retrospective studies, comparative study and literature review. Dexmedetomidine has been increasingly used for sedation in patients with autism spectrum disorder, mainly due to their lack of collaboration with health professionals. Among the main side effects arising from its use, there is a decrease in respiratory rate, as well as a reduction in blood pressure. Its use has been beneficial as it provides an important absence of agitation, as well as combativeness or anger during the recovery phase.* ***Conclusion:*** *The use of Dexmedetomidine is feasible for the sedation of patients with autism spectrum disorder if there is a good accessibility to the medication. It is essential that a comprehensive anamnesis and continuous monitoring be carried out throughout the procedure.*

Keywords*: Dexmedetomidine, Autism spectrum disorder, Sedation, Autism.*

Resumo

Introdução: *Dexmedetomidina é considerado um medicamento promissor utilizado para sedação nas mais variadas áreas de saúde. Considerada um agonista α-2 central, seu uso é seguro graças à presença de depressão respiratória mínima.* ***Objetivo:*** *Este estudo tem como objetivo realizar uma revisão da literatura sobre os efeitos da sedação com o uso de Dexmedetomidina em pacientes portadores do transtorno do espectro autista. Métodos: Para adequada análise, desenvolveu-se uma estratégia de revisão de literatura nas bases de dados Pubmed (MEDLINE), Scielo, Cochrane e Google Acadêmico. Foram incluídos artigos em inglês publicados entre 2008 e 2019.* ***Resultados:*** *Foram selecionados 9 artigos, os quais incluem relatos de casos, estudos prospectivos e retrospectivos, estudo comparativo e revisão de literatura. A Dexmedetomidina tem sido cada vez mais utilizada para sedação em pacientes com transtorno do espectro autista, principalmente devido à falta de colaboração dos mesmos com os profissionais da saúde. Dentre os principais efeitos colaterais advindos de seu uso, destacam-se diminuição da frequência respiratória, assim como redução da pressão arterial. Seu uso tem sido benéfico pois fornece uma importante ausência de agitação, assim como combatividade ou raiva durante a fase de recuperação.* ***Conclusão****: A utilização da Dexmedetomidina é viável para a sedação de pacientes com transtorno do espectro autista desde que haja boa acessibilidade à medicação. É imprescindível que seja realizada uma ampla anamnese e monitorização contínua ao longo do procedimento.*

Palavras chave*: Dexmedetomidina, Transtorno do espectro autista, Sedação, Autismo.*

Introduction

Dexmedetomidine (DEX) is considered a promising drug used for sedation in various healthcare areas[1]. Considered a central α-2 agonist, its use is safe due to the presence of minimal respiratory depression[1]. In addition, it presents important advantages such as a decrease in agitation during the execution of various procedures, a shorter extubation time, and

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a reduction in the need for opioids in the postoperative period[2]. Patients with autistic spectrum disorder (ASD) are characterized by the presence of communication deficits, interest restriction and repetitive behaviors[3]. Agitation and resistance are striking traits of these patients, often making medical/dental treatment impossible exclusively through conditioning This is one of the reasons why there is the need for an approach through an effective sedative regimen[4]. It is reported in the literature a variety of sedatives already used, such as nitrous oxide, propofol, opioids, ketamine, midazolam (MDZ) among others [5]. Despite this, the use of each regimen presents important points that should be emphasized. It is known that, for example, intramuscular (IM) ketamine presents an adequate action of use and considerable bioavailability, however, an administration that may require caution due to the need for physical proximity[6]; MDZ, on the other hand, presents positive aspects such as anxiolysis and reduction of postoperative vomiting, but some undesirable reactions, such as behavioral disinhibition and restlessness [7-8]. Therefore, DEX has gained an important prominence in this scenario, since it comprises an adequate safety profile and has relevant sedative, analgesic, and anxiolytic effects. However, among its adverse effects, related to the dose and age group administered, we can observe a prominent picture of bradycardia, atrial fibrillation, nausea and change in mean blood pressure (BP) [9-12]. This study has as main objective to verify through a literature review the use of DEX for sedation in patients with ASD.

Method

A literature review was conducted in MEDLINE databases, through PubMed; Cochrane, Scielo, Web of Science and Google Academic using the combination of the following terms: "Dexmedetomidine" and "Autism Spectrum Disorder", "Dexmedetomidine" or "Autism Spectrum Disorder", "Autism Spectrum Disorder" and "Sedation", "Autism Spectrum Disorder" or "Sedation", "Autism" and "Sedation". The search was conducted in May 2020.

As inclusion criteria, the following items were assessed: articles published in English from 2008 on; selected only randomized clinical trials, systematic reviews, literature reviews, retrospective studies, clinical trials, and comparative studies. As exclusion criteria, studies that did not fit the proposed criteria were eliminated after reading the title, abstract and full text.

Tables were created to help visualize the information contained throughout this article and to summarize the results. Table 1 shows the search process for the methodological selection of the studies.

Table 1

Search process for methodological selection of studies.

Electronic database search	MEDLINE, through PubMed; Cochrane, Scielo, Web of Science and Google Academic
Descriptors used in combination	"*Dexmedetomidine*" and "*Autism Spectrum Disorder*", "*Dexmedetomidine*" or '*Autism Spectrum Disorder*", "*Autism Spectrum Disorder*" and "*Sedation*", "*Autism Spectrum Disorder*" or "*Sedation*", "*Autism*" and "*Sedation*"
Search period	May 2020
Inclusion criteria	Language in English, from 2008 Selected: randomized clinical studies, systematic reviews, literature review, retrospective studies, clinical trial, and comparative study
Exclusion criteria	They did not fit the proposed theme afterwards: - Reading titles and abstracts and the full text

Results

Initially, 176 articles were found. After applying the established inclusion criteria, 38 studies were selected. After excluding duplicates and reading the abstract, 23 studies were removed. Of these, 6 studies were removed after full reading, and finally, 9 scientific articles were included.

The articles are listed in Tables 2 and 3 according to the type of study.

DEX has been increasingly used for sedation in patients with ASD, mainly due to their lack of cooperation with health professionals[7,9]. Among the most varied situations that require its use, are dental procedures and imaging and monitoring exams, such as Magnetic Resonance Imaging (MRI)[11,9] and the Electroencephalogram (EEG) respectively[12,8].

In the studies addressed, most of the use of DEX was in young patients. In the study of Lubisch et al[17], the youngest patient among the studies was approached, with 8 months of life. In this study, the authors report that younger patients need approximately 20% more of the drug compared to older children. Only one case of respiratory obstruction was reported in the study [17].

Due to the potential to suppress seizures in the EEG examination, sedatives such as benzodiazepines, barbiturates and propofol are not recommended in this type of procedure[17]. The use of DEX, as an alternative for these cases, has been a considerable option. Nevertheless, we must emphasize that among some of its side effects, the decrease in respiratory rate and BP, as in the study by Ray, Tobias[16].

Table 2

Case reports, retrospective studies and comparative study.

Authors (Year)/ Country	*Sample*	*Methodology*	*Results*
Konia (2016)[6]/ United States	ASD: N=1 Dental procedure: Dental caries	Case report	Age: 20 years Male with 86 kg, 183 cm severe autism and developmental delay; no previous medical history. Despite difficult physical contact, the patient was using oral medication (previous unpleasant experience with IM ketamine and MDZ orally at a dose of 0,35 mg/kg did not have the desired effect). Initially, DEX orally (5 mg/kg) was used for this reason and to prevent vomiting episodes. To prevent possible physical aggression, MDZ (2 mg), fentanyl (1 mcg/kg), lidocaine (1 mg/kg) and rocuronium (0,6 mg/kg) were subsequently administered IV. Less emergency delirium and vomiting When compared to ketamine. Few side effects were present.
Stuker et al (2018)[13]/ United States	ASD: N=1 Dental procedure: Dental restoration	Case report	Age: 8 years DEX IN (3mg/kg) Absence of bradycardia, hypotension, transient hypertension, respiratory depression, or belligerence Absence of disinhibition or hyperactivity
Fernandez (2018)[14]/ Spain	ASD: N=1 Dental procedure: Dental extraction	Case report (Letter to the Editor)	Age: 10 years DEX EV bolus of 0,5 µ/kg plus followed by 0,3 µ/kg/H Absence of cardiac abnormalities Hemodynamically stable
Carlone et al (2019)[15]/Italy	ASD: N = 8 Emergency procedures	Case series	Age: 5 to 14 years DEX IM (4 ug/kg) Absence of bradycardia or hypertension Absence of other adverse effects
Ray, Tobias (2008)[16]/ Colombia	ASD: N=42 Electroencephalogram	Retrospective study	Age: 2 to 11 years DEX IV (0,5 to 3,5 ug/kg) DEX orally (5,6 mg/kg) Decreased HR and BP in all patients Absence of agitation or excitement during recovery from sedation
Lubisch et al (2009) [17]/United States	ASD and neurobehavioral disorders: N =315 Magnetic Resonance Imaging	Retrospective Multicenter study	Age: 8 months to 24 years DEX diluted in saline solution (0,9%) to a final concentration of 4 mg/mL (orally/IV or orally + IV) MDZ varied among the subjects evaluated: 0.08 ± 0.09 mg/kg IV (n = 213), 0.45 ± 0.20 mg/kg orally (n = 137) or 0.30 ± 0.16 mg/kg IN (n = 9) DEX: sedation achieved in 32/315 patients (10,2%) and in 283/315 patients (89,8%) who received adjunctive MDZ. 1 case of respiratory obstruction only.

Table 2

Case reports, retrospective studies and comparative study.

Authors (Year)/ Country	*Sample*	*Methodology*	*Results*
Li et al (2019)[3]/ China	ASD (suspect): N=278 CT and/or ABR	Comparative study	Age: 9 to 12 years DEX IN (3 µg/kg) DEX IN (3 µg/kg) + MDZ Hypotension (N=5) and absence of bradycardia Absence of desaturation and respiratory problems, gastrointestinal upset (N=2), Agitation (N=2), Hyperactivity (N=3), Motor imbalance (N=4) and febrile illness (N=1) The association of DEX IN + MDZ presents a statistically higher success rate (83,5%) and absence of major adverse effects. Similarly, a shorter time to return to normal activities was observed when this combination was used (5.7 hours); when only DEX IN was used: 6.0 hours
Abulebda et al (2018)[19]/United States	ASD: N= 56 Magnetic Resonance Imaging	Retrospective study	Age: Not mentioned DEX IV (bolus of 2 mg/kg initially, followed by maintenance dose of 1 mg/kg/h) Propofol (1 mg/kg – up to a maximum of 50 mg) + continuous infusion of (83 mg/kg/min) DEX provided better hemodynamic stability (preservation of BP and HR) Propofol provided faster sedation onset, recovery, and discharge times. DEX could be a suitable alternative sedative agent to propofol in these patients.

Legend: ASD: Autistic Spectrum Disorder, DEX: Dexmedetomidine, IM: Intramuscular, IN: Intranasal, IV: Intravenous, MDZ: Midazolam, HR: Heart rate, BP: Blood pressure, CT: Computed Tomography, ABR: Auditory brainstem response.

Table 3

Literature review.

Authors (Year)/Country	*Sample*	*Methodology*	*Results*
Keidan et al (2015)[18]/ Israel	N =183 kids (TEA: N= 44)	Narrative review	Age: 1 to 18 years DEX IV (12 µg.kg - 1.h -1) Chloral hydrate Ketamine Hypotension and Bradycardia Oxygen Desaturation (N=2)

Legend: DEX: Dexmedetomidine, IV: Intravenous.

The literature considers MDZ as the anxiolytic most used in preoperative situations. Despite its beneficial effects, such as sedation and anterograde amnesia, it presents some unwanted effects, such as restlessness and behavioral disinhibition[13]. The use of DEX, in the most varied situations, demonstrates an important absence of agitation, as well as combativeness or anger during the recovery phase[4,9].

In the study of Keidan et al[18], oxygen desaturation was a feature mentioned because of DEX use in two patients in question. Despite the event, satisfactory EEG recordings were noted in all those submitted to the exam[18]. Two reports of apnea were reported: in one patient who received DEX and in another who received propofol. Despite the apnea episode, no interventions were required, and the MRI exams were successfully completed.

Gastrointestinal disturbance and febrile illness were effects found due to DEX use in patients with ASD [3]. In the study of Konia et al[6] and Abulebda et

al [19] there were no reports of nausea and vomiting during dental procedures and imaging exams.

Discussion

The present study is justified by the presence of few reports in the literature that show the potential effect of the use of DEX in patients with ASD, highlighting its main repercussions in the most diverse situations in which its applicability is necessary. There are limitations in comparative and prospective studies on the subject.

The medical/dental care of patients with ASD undergoing sedation is considered challenging. This is due to the characteristics of ASD itself, where it is even more necessary to apply agents that have a rapid onset and recovery phase, with the presence of minimal side effects and safety during and after the procedure performed[21]. In the study of Konia et al[6], for example, the selection for DEX was due to two factors: patient diagnosis and previous failure with IM Ketamine and MDZ orally (0,35 mg/kg).

In the study of Abulebda et al[19] it is reported that the use of DEX in contrast to the use of propofol as a sedative agent in the performance of MRI causes better preservation of BP and maintenance of heart rate. In the study, it is reported that 39% of the patients who used propofol presented hypotension, and only in 3.6% who used DEX, this condition was observed[19]. According to Ebert et al[22], DEX has a lower respiratory depressant effect compared to other sedatives. The results of this review show that the use of DEX presented episodes of respiratory alteration in three observed studies.

In the study of Lubisch et al[17], only 1 case of upper airway obstruction was observed after administration of DEX (0,5 mg/kg) due to failure with sedation with MDZ orally (0,5 mg/kg), MDZ IV (0,3 mg/kg) and sodium pentobarbital (4,0 mg/kg). It is important to emphasize that the patient received the necessary care and there were no major complications.

The use of DEX, evidenced in the study of Lubisch et al[17], provides similar effects to clonidine in patients with ASD when performing EEG. With a shorter recovery time and sedation, it is considered a good alternative for use in this group of patients [17]. The main observation of the authors, as well as in the study of Abulebda et al[19] is the exacerbated value of DEX compared with other sedatives, such as clonidine and propofol[17, 19]. The financial benefit of its recurrent administration is explained by some authors, due to the impacting effect of rapid action and efficiency throughout sedation[23].

In the studies evaluated, the youngest patient with ASD who underwent sedation with DEX was eight months old[17]. The age groups mentioned throughout this review present evident heterogeneity. In the studies of Li et al[4] and Yuen et al[24], it was found that the way DEX is administered influences patient tolerability. It is also important to note that in the study of Li et al[4], a shorter time of return to activities was observed when IN DEX alone was used. This data emphasizes an important aspect related to this age group, together with an adequate safety profile and absence of associated unpleasant sensation.

The limitations of this study are related to the increasing use of DEX in various situations, with generalized data about the form of administration in each procedure addressed. These directly influence the number of articles selected, as well as the results obtained, which often become nonspecific for the group of patients studied.

Conclusion

Through this study we conclude that the use of DEX is feasible for the sedation of patients with ASD if there is good accessibility to the medication. It is essential that a broad anamnesis and continuous monitoring be performed throughout the procedure.

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