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Dexmedetomidine versus midazolam sedation for autistic children undergoing electroencephalogram: a prospective randomized trial

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Abstract

Background: Dexmedetomidine procedural sedation for pediatric patients undergoing radiological imaging has proved to be effective and safe.

Objective: We compared the efficacy of outpatient sedation with intravenous dexmedetomidine versus intravenous midazolam in autistic children undergoing electroencephalogram.

Patients and methods: Forty pediatric autistic patients aged 6–11 years old undergoing electroencephalogram were studied. In the dexmedetomidine group, patients received a loading dose of IV dexmedetomidine 1 μg/kg slowly over 10 min followed by an IV infusion of dexmedetomidine 0.7 μg/kg/h stopped when Ramsay sedation score (RSS) reached 4. In the midazolam group (n = 20), patients received induction with a loading dose of 0.05 mg/kg midazolam given over 2 min, then wait another 2 to 5 min to evaluate the sedative effect. Additional doses of IV midazolam (0.05 mg/kg) were given until we reached RSS reached 4.
Sedation score, induction time, recovery time, behavioral scores, parents' satisfaction scores, success rate, oxygen saturation, and the incidence of complications as bradycardia and attacks of agitation were recorded.

Results: Dexmedetomidine was associated with shorter induction and recovery times(< 0.001) and higher percentage of oxygen saturation compared with midazolam group (P < 0.001).
The dexmedetomidine group showed higher sedation and behavioral scores as well as success rate compared with midazolam. Parents' satisfaction scores were significantly higher in the dexmedetomidine group. The incidence of agitation was significantly higher in the midazolam group compared with the dexmedetomidine group (p = 0.035).

Conclusion: Dexmedetomidine is a feasible sedation technique in autistic children undergoing outpatient electroencephalogram in terms of faster recovery and less incidence of complications.

Keywords: Dexmedetomidine, Midazolam, Autism, Pediatric, Sedation, EEG

Introduction

Autism seems to be a rising problem (Myers & Johnson, 2007). Luckily, there is increased interest in the treatment of neurologic morbidities in these patients (Tuchman, 2000; Canitano et al., 2005). For this reason, proper diagnosis using electroencephalogram (EEG), magnetic resonance imaging, or both is mandatory for this patient population (Li et al., 2017). Initially, running these diagnostic procedures in these children is considered challenging (Mehta et al., 2004a; Pisalchaiyong et al., 2005), so an effective sedation technique is needed to obtain clear data. Earlier, some anesthetic agents such as barbitates and ketamine are used but they result in agitation during recovery (Greenberg et al., 2000; Strain et al., 1988) Mostly, chloral hydrate is used for sedation during electroencephalogram, but its failure rate and adverse behavioral reactions, particularly agitation, are common in children with neurobehavioral disorders, making physicians more keen to search for better options (Berkenbosch et al.,

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2005a). Dexmedetomidine (trade name, Precedex) is a selective a2-adrenoreceptor agonist with increasing popularity in procedural sedation (Berkenbosch et al., 2005b; Mason et al., 2008). It has greater affinity for the alpha 2 than alpha 1 receptors (Virtanen et al., 1988); therefore, fewer hemodynamic and neurologic side effects happen (Rutman, 2009; Gertler & Brown, 2001) making it an attractive choice for sedation of autistic patients. It is characterized by its rapid onset and elimination, so it is conveniently used in day case procedures (Myers & Johnson, 2007).

Midazolam is a water-soluble benzodiazepine used for sedation of pediatrics with neurologic disorders. It can be co-administrated with other sedatives and it is administered through various ways as intravenous or intramuscular routes. Occasionally, big doses of midazolam result in adverse events such as nausea, vomiting, and respiratory depression (Lubisch et al., 2009).

Aim

The aim of this study was to compare outpatient sedation using either intravenous dexmedetomidine or intravenous midazolam as regards induction, recovery times, parents' satisfaction, and incidence of complications in autistic children undergoing EEG.

Patients and methods

After the approval of the medical ethics committee of Ain Shams University number FMASU R 11/2018, this prospective randomized parallel group study was conducted over 40 patients between the age of 6–11 years old, physical status I and II according to the American Society of Anesthesiologists (ASA), undergoing electroencephalogram at Ain Shams University hospitals, after obtaining written informed consents from the guardians of the children.

Preoperative evaluation included a detailed history, physical examination along with investigations, including complete blood count and chest x-ray. The subjects were fasting for 2 h for clear fluids and 6 h for meals.

Exclusion criteria

Patients with cardiovascular instability, hepatic or renal impairment, metabolic or any other systemic diseases, those suffering from severe congenital heart diseases or pulmonary hypertension, or trauma of the head, gastroesophygeal reflux, patients with respiratory infection, allergy to the drugs used in the current study, refusal of parents to participate and patients using pain killers were excluded from the study.

Preparation of the study drugs

Dexmedetomidine (precedex 200 μg per 2 ml, Abbott laboratories, Abbott park, IL, USA), the dexmedetomidine (100 μg/ml) was adjusted to 1 μg/ml by diluting 0.5 ml of dexmedetomidine in 49.5 ml normal saline.

Midazolam (Dormicum 5 mg/5 ml; Roche Basel, Switzerland) diluted in 20 ml saline 0.9% IV given very slowly over 2 min.

The anesthetic technique

On arriving to the induction room, the anesthesiologist secured 22 G cannula before the start of sedation facilitated by EMLA cream and atropine 0.01 mg/kg was administered in addition to 20 ml/kg ringer acetate which was infused. Intraoperative standard monitors as ECG, non-invasive blood pressure (Dash 5000; General Electric, Medical Systems Information Technologies, Inc., Tower Ave., Milwaukee, WI, USA) and pulse oximetry were placed, supplemental oxygen 3 L/min was given via nasal pronges. A separate intravenous line was inserted for the sedative drugs, a bolus dose of the sedative can cause apnea or airway obstruction so all airway equipment, like nasal or oral airways, laryngeal mask, endotracheal tube, and laryngoscope of different sizes were available before sedation.

Randomization

Patients were randomly divided into two parallel groups by a computer-generated number lists and by sealed envelope technique. Allocation of patients to either group was done by a clinician not involved in the study.Dexmedetomidine (Dex) group (n = 20)

Patients received induction with a loading dose of IV dexmedetomidine 1 μg/kg diluted in 20 ml saline which was given slowly over 10 min followed by an IV infusion of dexmedetomidine 0.7 μg/kg/h (0.7 ml/kg/h) until RSS reached 4 then dexmedetomidine infusion was stopped. Rescue sedation inform of top up doses of propofol 0.5/kg mg IV was administered over 5 min if RSS < 4.

Midazolam (Mid.) group (n = 20)

Patients received induction with a loading dose of 0.05 mg/kg midazolam (Dormicum 5 mg/5 ml; Roche Basel, Switzerland) given very slowly over 2 min, then wait for another 5 min to fully evaluate the sedative effect (Ramsay sedation score of 4), and then additional 0.05 mg/kg doses of midazolam until we reached the desired RSS of 4, keeping in mind that the maximum total dose of midazolam should not exceed 0.4 mg/kg (10 mg). Rescue sedation in form of top up doses of propofol 0.5 mg/kg IV was administered over 5 min if RSS < 4.

Primary outcome measures

Primary outcome measures included the following:

Recovery time: The elapsed time elapsed from discontinuation of the study drugs (RSS reached 4) till the point at which RSS of 2 was reached.

Secondary outcome measures

Secondary outcome measures included the following:

Induction time: Time in minutes elapsed from the initial administration of the study drug (loading dose) till reaching RSS of 4.

Assessment of the level of sedation using RSS every 5 min, where 1 is awake and anxious; 2, drowsy; 3, arousable to verbal commands; 4, asleep with brisk response to stimulus; 5, asleep with no response to stimulus; and 6, deep sleep. A score of 4 was considered satisfactory. The first three levels were called awake levels and the last three were called asleep levels. RSS 4 is a clinically acceptable depth of sedation sufficient to facilitate diagnostic imaging.

The quality of EEG was evaluated using 3-point scale (1 = no motion, 2 = slight movement, 3 = marked movement required repetition of EEG).

Oxygen saturation was monitored continuously throughout the procedure. Frankl behavioral scores was assessed every 5 min on a 4-point scale to check child attitude during the whole EEG session (Done et al., 2016) where 1 is definitely negative (moving forcefully, totally uncooperative); 2, negative (anxious, negative attitude, and difficult to perform the procedure); 3, positive (the child accepts the treatment and minimal movement); and 4, definitely positive (quiet, calm, no movement).

Parent satisfaction: The parents were asked to rate their level of satisfaction with the sedation protocol on a 4-point satisfaction scale as follows: 1, very satisfied; 2, satisfied; 3, neutral; 4, unsatisfied.

Adverse events: (1) Bradycardia was considered when heart rate drops by 25% or more from the baseline values (Koroglu et al., 2006) and bradycardia was managed by bolus dose of atropine 0.02 mg/kg IV or if it was transient, it did not need treatment. (2) Incidence of emergence agitation was all recorded. If any of the patients develop complications such as cardiac arrest, apnea, or laryngospasm, the patient is ventilated manually using mask and bag ventilation, if failed, endotracheal intubation followed by mechanical ventilation was done. Additionally, in cardiac arrest, increments of epinephrine were given every 3 to 5 min, followed by cardiopulmonary resuscitation and they were excluded from the study

A failed sedation: Inadequate sedation to successfully complete the procedure and to obtain good quality images of diagnostic value after receiving the maximum allowable doses per sedation protocol because of motion or sedation score does not reach 4 despite repeated doses or infusion of the study drugs. In this case, a rescue sedation in form of top up doses of propofol 0.5 mg/kg IV over 5 min. The procedure time was defined as the duration from reaching the targeted RSS till the end of the procedure.

At the end of the procedure, all the patients were transferred to the post-anesthesia care unit (PACU) where they were monitored by an experienced nurse. Finally, patients were considered ready for discharge when they had stable vital signs, were oriented, were able to ambulate unassisted, and had no vomiting attacks.

Statistical methods

Using Power Calculations and Sample Size software (PASS; NCSS, LLC, East Kaysville, UT, USA) for sample size calculation, we are setting alpha error at 5% and power at 95%. Depending on a previous study (Lubisch et al., 2009) showed that the mean recovery time among the midazolam group was 117 ± 41 and for the dexmedetomidine group it was 69 ± 34 min. Based on this and taking into consideration 20% drop out, we needed to enroll 20 patients in each group to reject null hypothesis.

The statistical analysis was performed using SPSS software package version 17 (Chicago, IL, USA). Normally distributed numerical data were presented as mean ± SD and differences between groups were compared using the independent Student's *t* test, data not normally distributed were compared using Mann-Whitney test and were presented as median (IQR) and categorical variables were analyzed using the χ^2 test or fisher exact test and are presented as number (%).

Results

A total of 40 patients were assessed for eligibility. The CONSORT flow chart (Fig. 1) showing the progress of patients through various stages of the study. A total of 40 patients were randomized and completed the trial, and their data were analyzed.

The patient demographic data, age, weight, sex, and procedure time, were comparable in both groups (Table 1).

The intention to treat analysis of the primary outcome revealed that the recovery time was significantly longer in the midazolam group (32.97 ± 2.6 min) compared with the dexmedetomidine group (23.2 ± 1.74), $p < 0.001$* (Table 1). The induction time was significantly longer in the midazolam group compared with the dexmedetomidine group ($p < 0.001$*) (Table 1). Oxygen saturation was significantly higher in the dexmedetomidine group compared with the midazolam group, ($p < 0.001$*) (Table 1). Post-sedation behavioral scores were significantly higher in the dexmedetomidine group compared with the midazolam group, ($p < 0.001$*) (Table 1).

There was no significant difference regarding sedation scores between the study groups at 5, 20, and 25 min of the start of the procedure ($p < 0.001$*) (Table 2).

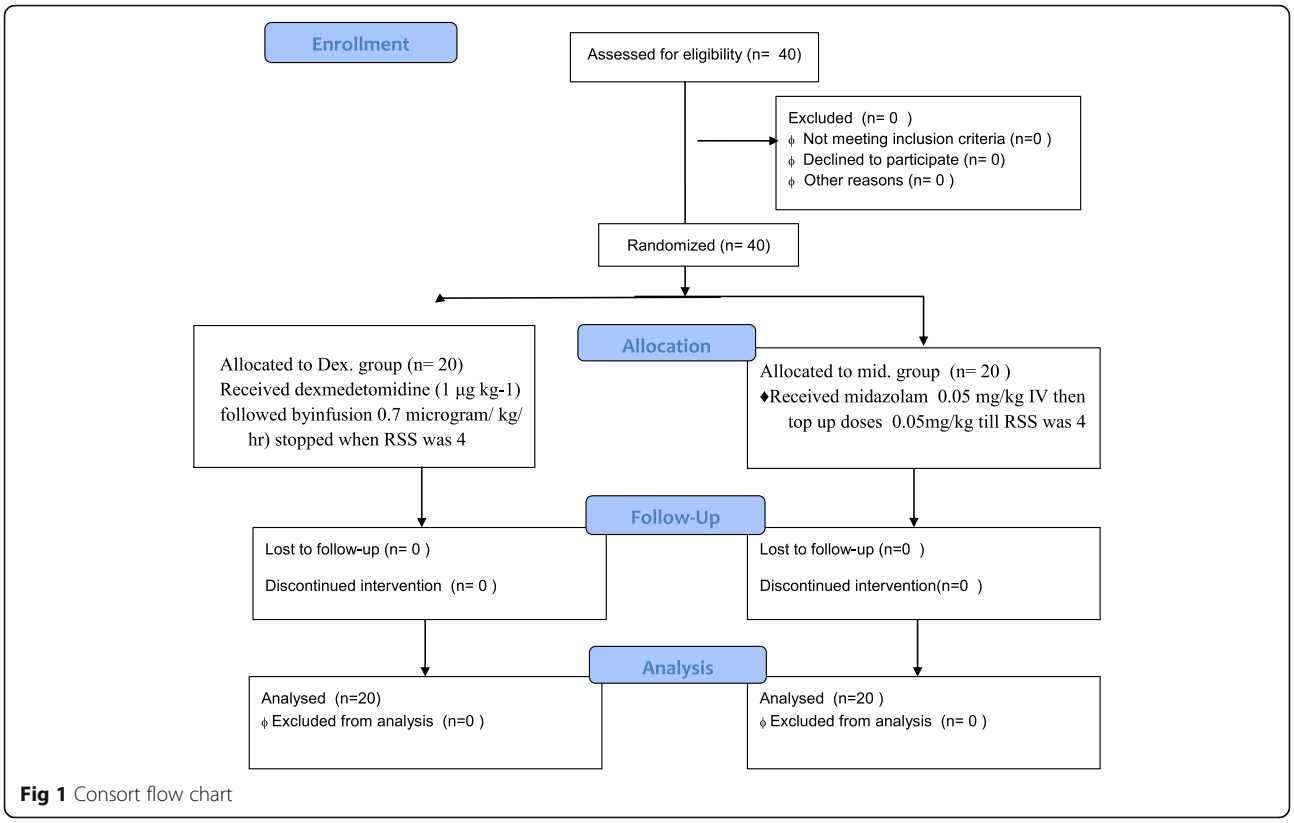

Fig 1 Consort flow chart

Sedation scores were significantly higher in the dexmedetomidine group compared with the midazolam group at 10 and 15 min (Table 2).

The success rate was significantly higher in the dexmedetomidine group compared with the midazolam group ($p < 0.008$) (Table 3). Parent satisfaction scores were significantly better in the dexmedetomidine group compared with the midazolam group (Table 3).

There was no significant difference between the study groups regarding the incidence of bradycardia (Table 4). The incidence of agitation was significantly higher in the midazolam group compared with the dexmedetomidine group, ($p = 0.035$) (Table 4).

Table 1 Comparison of demographic data, procedural duration, post-sedation behavioral scores, induction time, recovery time, and oxygen saturation

	Dex group $n = 20$	Mid group $n = 20$	*P* value
Sex			
Female	8 (40%)	7 (35%)	0.744
Male	12 (60%)	13 (65%)	
Weight			
Range	21–29	20–30	0.329
Mean ± SD	23.45 ± 2.67	22.47 ± 3.54	
Age (years)	7.94 ± 1.77	8.03 ± 1.7	0.871
Procedure time (min)	26.7 ± 3.3	26.46 ± 3.1	0.813
Post-sedation behavioral scores	4 (3–4)	2 (2–3)	< 0.001**
Induction time (min)	11.9 ± 1.53	22.3 ± 2.07	< 0.001**
Recovery time (min)	23.2 ± 1.74	32.97 ± 2.6	< 0.001**
Oxygen saturation (%)	96.76 ± 1.5	93.3 ± 1.08	< 0.001**

All data were presented as mean ± SD except sex was presented as percentage
**highly significant

Discussion

An electroencephalogram (EEG) is best done when the patient is awake but this makes the procedure difficult for radiologists especially in children with neurodevelopmental disorders including those with autism (Folayan

Table 2 Comparison of sedation scores between the study groups

	Sedation scores		*T* test	
	Dex group ($n = 20$)	Mid group ($n = 20$)	*t*	*P* value
5 min	1.55 ± 0.51	1.61 ± 0.47	0.387	0.701
10 min	3.65 ± 0.49	3.3 ± 0.47	2.307	0.027*
15 min	3.7 ± 0.47	3.24 ± 0.44	3.111	0.004*
20 min	3.15 ± 0.67	3.2 ± 0.7	0.231	0.818
25 min	2.95 ± 0.69	3 ± 0.73	0.224	0.824

All data were presented as mean ± SD
*significant

Table 3 Comparison of success rate and satisfaction scores between the study groups

Success rate and satisfaction scores	Dex group $n = 20$	Mid group $n = 20$	*P* value
Success rate (adequate sedation)	11 (55%)	3 (15%)	0.008*
Satisfaction scores	1 (1–2)	2 (2–3)	< 0.001**

Satisfaction scores were presented as percentage; success rate was presented as median
*significant
**highly significant

et al., 2002). Dexmedetomidine is a feasible option as it causes satisfactory degrees of sedation resembling natural sleep in addition to smooth recovery with minor complications (Folayan et al., 2002).

The results of this randomized prospective study showed that outpatient sedation with IV dexmedetomidine was effective and safe as it was associated with shorter induction and recovery times, and better parent's satisfaction scores with less incidence of complications, which enabled the recording and interpretation of EEG in our patients.

In an earlier work by Al-Taher (Al, 2016) and his colleagues discussing pediatric procedural sedation done using either dexmedetomidine or midazolam-propofol, they noticed that the recovery time was significantly shorter in the dexmedetomidine group compared to the midazolam-propofol group (18.3 ± 5.9 versus 25.2 ± 8.2 min, respectively, $p < 0.0004$); this supports our findings but oxygen saturation was comparable in the two groups, this differs from our results which showed significant difference between the study groups.

In a study by Kamal et al. who tested the efficacy of dexmedetomidine (D) versus propofol (P) for pediatric sedation undergoing MRI, they stated that the induction and recovery times were much longer in the dexmedetomidine group, only 2 of 60 patients experienced bradycardia as regard group D, and hemodynamic instability and oxygen desaturation were unremarkable in both groups. Their findings differ from ours; this may be due to the difference in the sample size or the use of higher loading dose of dexmedetomidine 2.0 μg/kg and higher infusion rate 1.0 μg/kg/h (Kamal et al., 2017).

Mehta and her friends revealed that clonidine sedation used in autistic children undergoing electroencephalography was satisfactory to produce high quality radiological images and it was associated with shorter induction and recovery times which were similar to results of our study (Mehta et al., 2004b).

Table 4 Comparison of the incidence of complications between the study group

Incidence of complications	Dex group $n = 20$	Mid group $n = 20$	*P* value
Bradycardia	7 (35%)	2 (10%)	0.058
Attacks of agitation	0 (0.0%)	4 (20%)	*0.035

All data were presented as percentage

Nelson et al. showed that dexmedetomidine mimic physiologic sleep and did not alter EEGs in contrast to other sedative agents in rodent studies (Nelson et al., 2003).

A similar study by Koroglu et al. showed that the success of sedation for children aged from 1to 7 years undergoing MRI was 80% in the dexmedetomidine group and 20% in the midazolam group, for both groups and heart rate values were comparable between the two groups (Koroglu et al., 2005). The results of this study agreed with our study.

A retrospective study on autistic children receiving dexmedetomidine for sedation showed that the incidence of bradycardia in patients receiving dexmedetomidine was significantly higher but transient which were similar to the results of our study (Lubisch et al., 2009).

A retrospective study by Ray and his colleagues done on children aged between 2 and 11 years old undergoing EEG analysis where they received dexmedetomidine for procedural sedation. Recovery was uneventful without incidence of agitation, also oxygen saturation remained above 92% in all patients and there was a transient drop in the heart rate values (Ray & Tobias, 2008). That study partially agreed with our study.

Babbitt et al. showed that dexmedetomidine is a reliable method of sedation for children with autism undergoing encephalography, there was significant decrease in heart rate in the dexmedetomidine group ($p = 0.007$) which is a well-recognized side effect of alpha 2 agonists (Babbitt et al., 2015). This study agreed with the results of our study.

A study by Berkenbosch and his colleagues showed that dexmedetomidine is better than other sedatives especially for autistic children posted for EEG alone or EEG followed by MRI or MRI only in the form of sufficient parents' satisfaction scores, smooth recovery with no complications as agitation (Berkenbosch et al., 2005c).

On the contrary to our results, Pandharipande et al. (Pandharipande et al., 2007) reported that dexmedetomidine sedation was associated with longer recovery time compared to lorazepam.

Dexmedetomidine has sedative, and anxiolytic, sympatholytic with minimal complications as nausea and vomiting (Gerlach & Dasta, 2007).

Previous studies showed that IV infusion of dexmedetomidine 0.4–0.7 μ/kg/h provides adequate procedural sedation so they were a guide for us to choose the study drug dose (Dere et al., 2010).

After reviewing the literature, we found that RSS of 4 was found satisfactory to facilitate painless diagnostic procedures as EEG (Sethi et al., 2014).

Limitations

The major limitation of our study was the lack of blinding as it leaves the trial open to criticism of observer bias. The sample size is relatively small so further studies are needed to confirm these findings as it is really an alarming problem.

Conclusions

Dexmedetomidine is a feasible sedation technique in autistic children undergoing outpatient electroencephalogram in terms of faster recovery and less incidence of complications.

Abbreviations

ASA: American Society of Anesthesiologists; dex: Dexmedetomidine; ECG: Electrocardiography; Mid.: Midazolam; NIBP: Non-invasive blood pressure; PACU: Post-anesthesia care unit; RSS: Ramsay sedation score; SDs: Standard deviations

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Authors' contributions

Idea, data collection, data analysis, and manuscript editing was done by the two authors. Both authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was done after institutional ethical committee approval from Ain-Shams University with the committee's reference number FMASU R 11 / 2018. Consent to participate was obtained from the guardians of the patients for inclusion in this study/requirement for consent was waived by the ethical committee.

Consent for publication

A consent to publish has been obtained from the participant to report individual patient data.

Competing interests

The authors declare that they have no competing interests.

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