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Intranasal dexmedetomidine versus intranasal midazolam as a premedication in pediatrics undergoing upper GI endoscopy

Dexmedetomidina intranasal versus midazolam intranasal como premedicación en pacientes pediátricos sometidos a endoscopia digestiva alta

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ABSTRACT

Background: Upper GI endoscopy is a common procedure performed in pediatric. Reducing peri-operative anxiety is a crucial concept for the pediatric anesthesiologist. Anxiety can give aggressive responses and make difficulty on postoperative pain control. Pre-anesthetic medication should focus on reducing this anxiety and psychological trauma and to assist the induction of anesthesia with rapid recovery. The aim of this work is to compare the effectiveness of intranasal dexmedetomidine and midazolam as a premedication in sedation of preschool children in upper Gastro-intestinal (GI) endoscopy. **Patients and Methods:** 70 pediatric patients scheduled for upper GI endoscopy, aged 2 to 6 years old of both sex, with physical status ASA I - II. All patients were randomized into two groups: group M (Midazolam): 35 patients received intranasal midazolam (0.2 mg/kg) up to 5 mg -. Group D (dexmedetomidine): 35 patients received intranasal dexmedetomidine (1 microgram/kg), Intranasal 0.5 ml was administrated in each nostril 30 min before induction with monitoring of sedation level and oxygen saturation. Separation from the parent was recorded by Parental Separation Anxiety Scale (PSAS) and Onset of sedation was monitored by Modified RAMSAY Sedation Scale both recorded in preoperative holding area, Post-operative emergence delirium was monitored by Pediatric Anesthesia Emergence Delirium (PAED) and Agitation was recorded by pediatric sedation agitation scale (PSAS) both recorded in Post-anesthesia care unit (PACU). **Results:** In the present study, the children were early separated from parents in midazolam group when compared to the dexmedetomidine group 5.14 ± 1.77 min vs 17.49 ± 4.05 min respectively with p value < 0.001. Furthermore, children in dexmedetomidine group achieved significant lower parent separation anxiety, agitation, and delirium scores postoperatively in comparison to midazolam group with p value < 0.001. **Conclusion:** In children undergoing upper GI endoscopy, premedication with dexmedetomidine at a dose of 1 µg/kg resulted in reasonable sedation, better parent separation, and lower postoperative agitation and delirium compared to intranasal midazolam at 0.2 mg/kg. However, dexmedetomidine had a delayed onset of action.

Keywords: Pediatrics, upper GI endoscopy, premedication, sedation, intranasal dexmedetomidine, intranasal midazolam.

RESUMEN

Antecedentes: La endoscopia digestiva alta es un procedimiento común en pediatría. Reducir la ansiedad perioperatoria es crucial para el anestesiólogo pediátrico. La ansiedad puede generar respuestas agresivas y dificultar el control del dolor posoperatorio. La medicación preanestésica debe centrarse en reducir la ansiedad y el trauma psicológico, así como en facilitar la inducción anestésica y una rápida recuperación. El objetivo de este trabajo es comparar la eficacia de la dexmedetomidina y el midazolam intranasales como premedicación para la sedación de niños preescolares en la endoscopia digestiva alta. **Pacientes y Métodos:** 70 pacientes pediátricos programados para endoscopia digestiva alta, de 2 a 6 años, de ambos sexos, con estado físico ASA I-II. Todos los pacientes fueron aleatorizados en dos grupos: grupo M (midazolam): 35 pacientes recibieron midazolam intranasal (0,2 mg/kg) hasta 5 mg. Grupo D (dexmedetomidina): 35 pacientes recibieron dexmedetomidina intranasal (1 microgramo/kg). Se administraron 0,5 ml intranasales en cada fosa nasal 30 minutos antes de la inducción, con monitorización del nivel de sedación y la saturación de oxígeno. La separación de los padres se registró mediante la Escala de ansiedad por separación parental (PSAS) y el inicio de la sedación se controló mediante la Escala de sedación RAMSAY modificada, ambas

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registradas en el área de espera preoperatoria. El delirio de emergencia posoperatoria se controló mediante el Delirio de emergencia de anestesia pediátrica (PAED) y la agitación se registró mediante la Escala de agitación de sedación pediátrica (PSAS), ambas registradas en la Unidad de cuidados postanestésicos (PACU). **Resultados:** En el presente estudio, los niños del grupo de midazolam fueron separados precozmente de sus padres, en comparación con los del grupo de dexmedetomidina, con un tiempo de 5,14 ± 1,77 min frente a 17,49 ± 4,05 min, respectivamente, con un valor de $p < 0,001$. Además, los niños del grupo de dexmedetomidina presentaron puntuaciones significativamente menores de ansiedad por separación de los padres, agitación y delirio posoperatorios, en comparación con el grupo de midazolam, con un valor de $p < 0,001$. **Conclusión:** En niños sometidos a endoscopia digestiva alta, la premedicación con dexmedetomidina a una dosis de 1 µg/kg produjo una sedación adecuada, mejor separación de los padres y menor agitación y delirio posoperatorios, en comparación con midazolam intranasal a 0,2 mg/kg. Sin embargo, la dexmedetomidina tuvo un inicio de acción retardado.

Palabras clave: Pediatría, endoscopia gastrointestinal superior, premedicación, sedación, dexmedetomidina intranasal, midazolam intranasal.

Introduction

Pediatric patients are very anxious during perioperative period, it is challenging to anesthesiologist to reduce this stress to achieve success. Various options of medications are used as anti-stress premedication as midazolam and dexmedetomidine which are effective and safe.[1]. Several factors contribute to emergency agitation (EA) as preoperative anxiety, pre-school age, type of surgery like ENT and strabismus, pain and too rapid emergence. It is a multifactorial[2]. Intranasal drug route provides a rapid, painless and easy way for premedication drugs in children. Furthermore, it reach the central nervous system directly without first pass metabolism[3]. The drug acidity (midazolam pH: 3.5) may cause nasal irritation and pain in the distribution of trigeminal nerve. Makes administration of intranasal midazolam not easy to most children as it causes a uncomfortable sensation[4]. Although midazolam is widely used premedication in children, with high bioavailability reaching 55% if administrated intranasally. peak effect after 10-20 min after intranasal administration. It is adverse effects includes respiratory depression, , cognitive dysfunction , behavioral alterations and paradoxical reactions[5]. Also dexmedetomidine has a bioavailability 65% (35% - 93%) if administered intranasally with peak sedative effect around 30-45 min[6].

Dexmedetomidine stimulate alpha2 adrenergic receptors which decrease central sympathetic outflow (7). Thus, it causes sedation and has analgesic effect with minimal respiratory depression in term of "conscious sedation", which means that patient can co-operate while he is sedated. While midazolam is enhancing neuro inhibitory GABA receptors which produce sedation[8].

The aim of this work is to compare the effectiveness of intranasal route of dexmedetomidine and midazolam as a sedative premedication of preschool children during upper GI endoscopy. separation from the parent by Parental Separation Anxiety Scale (PSAS) is considered the primary outcome. The secondary outcomes include sedation onset, post-operative emergence delirium and agitation.

Patients and Methods

A prospective, randomized and double-blinded clinical trial was done after approval of institutional ethical committee in Ain Shams University Hospitals (FAMSU) and obtaining an informed written consent from parents and clinical trial registration No (NCT06181682). 70 children, aged 2 to 6 years old of both sex, with physical status ASA I - II, scheduled for upper GI endoscopy. Exclusion criteria were patients with previous behavioral disorders like ADHD and autistic patients, ASA III or more, difficult air way and prolonged procedure more than 50 min. Full dilated history and physical examination was taken from all patients, written informed consents were obtained from parents.

Patients divided into 2 groups randomly by using a computer-generated sequence. Group M (Midazolam): 35 patients received intranasal midazolam (0.2 mg/kg) up to 5 mg - from a preparation of 5 mg/ml and adding 0.9% normal saline for final volume of 1 ml. Group D (dexmedetomidine): 35 patients received intranasal dexmedetomidine (1 microgram/kg), from 100 mcg/ml preparation and adding 0.9% normal saline for final volume of 1 ml. For both drugs 0.5 ml is injected in each nostril in recumbent position at the preoperative holding area with monitoring of conscious level and Spo2. The study drugs was prepared in a ready-to-inject form by a separate anesthesiologist who was not involved in the study, this way neither the parent nor the anestesthiologist collecting data were aware by the type of medication being used. Onset of sedation is considered when a Modified RAMSAY Sedation Scale reached 3 points and patient was transferred to operating room. Parental Separation Anxiety Scale was measured, score 1-2 was satisfactory separation while a score of 3-4 was unsatisfactory separation.

Intraoperative settings include standard monitoring attached to all patients. Inhalational induction by sevoflurane and Intravenous access was applied when the child was adequately anesthetized. If there is difficulty on endoscope introduction or patient regained consciousness, 0.5 to 1.5 mg/kg propofol would be given titration till adequate level of anaesthesia is achieved again. Blood pressure, heart rate and Spo2 were continuously attached during the procedure, but recorded readings every 15 min were included in the study.

At the PACU, the patient were monitored for oxygen saturation, heart rate and rhythm, respiratory rate and conscious level. Patient's agitation score was calculated using pediatric sedation agitation scale (PSAS) and Pediatric Anesthesia Emergence Delirium (PAED) score was also calculated at PACU. Children with emergence delirium ≥ 12 were given 1 mcg/kg fentanyl.

Results

Seventy (70) patients were enrolled in the study, 35 patients in each group.

Groups were compared in demographic data (in terms of age, sex and BMI) and there were no statistically significant difference between groups (p-value > 0.05) (Table 1).

Groups were compared in terms of heart rate (HR), mean arterial blood pressure (mean BP), and oxygen saturation (Spo2) at intervals of basal,15,30,45 min and there were statistically significant difference between groups in HR and Mean BP at 30 min. (Table 2).

Groups were compared in onset of sedation and there was statistically significant difference between groups in onset of sedation (p-value < 0.001) (Table 3).

Groups were comparable in parental separation anxiety scale _PSAS_, paediatric anaesthesia emergence delirium _PAED, paediatric sedation agitation scale _PSAS_and there were statistically significant difference between groups (Table 4).

Discussion

Preschool patients undergoing procedures feel anxiety and distress during the perioperative period. Children at this age are usually uncooperative, fearful and anxious specifically during times of parental separation[9].

This study was done for 70 pediatric patients, 2-6 years old, scheduled for upper GI endoscopy.

Demographic data for both groups as regard (age, sex, and BMI) had no statistically significant difference.

Table 1. Comparison between groups as regard demographic data and procedure time

		Group M (n = 35)	Group D (n = 35)	p-value
Age (years)		4.51 ± 1.3	4.09 ± 1.2	0.155[t]
BMI		17.77 ± 2.79	17.34 ± 3.60	0.581[t]
Sex	Male Female	13 (37.1%) 22 (62.9%)	17 (48.6%) 18 (51.4%)	0.338χ^2
Procedure time		26.8 ± 7.3	27.5 ± 7.96	0.686[t]

Data expressed as mean ± SD; proportion; t = student t test; χ^2 = chi square.

Table 2. Comparison between groups as regard hemodynamic

	Group M (n = 35)	Group D (n = 35)	p-value[t]
Heart rate (basal)	100.74±13.10	106.89±15.97	0.083
Heart rate (15 min)	98.06±13.26	95.71±12.07	0.442
Heart rate (30 min)	94.91±11.46	88.86±10.22	0.023
Heart rate (45 min)	92.40±11.35	82.06±10.45	0.896
SPO2 (basal)	98.43±1.38	98.83±1.22	0.204
SPO2 (15 min)	97.74±1.42	98.06±1.39	0.353
SPO2 (30 min)	97.74±1.12	98.03±1.50	0.371
SPO2 (45 min)	98.40±1.09	97.97±1.20	0.123
Mean BP (basal)	71.89±10.94	72.97±10.02	0.667
Mean BP (15 min)	70.46±10.58	68.97±9.73	0.543
Mean BP (30 min)	69.40±10.45	58.03±9.20	< 0.001
Mean BP (45 min)	68.83±10.18	65.71±8.33	0.166

Data expressed as mean ± SD; t: = student t test.

Table 3. Comparison between groups as regard onset of sedatio

	Group M (n = 35)	Group D (n = 35)	p-value[t]
Onset of sedation (min)	5.14 ± 1.77	17.49 ± 4.05	< 0.001

Data expressed as mean ± SD; t: = student t test.

Table 4. Comparison between groups as regard PSAS, PAED, PSAS							
	Group M (n = 35)			Group D (n = 35)			p-value[m]
	Rang	Median	IQR	rang	Median	IQR	
Parental separation anxiety scale	1-4	3	2-3	1-3	2	1-2	< 0.001
Paediatric anaesthesia emergence delirium	7-12	9	9-10	0-14	3	2-8	< 0.001
Paediatric sedation agitation scale	2-5	4	3-5	1-5	3	2-3	< 0.001

Data expressed as median; IQR: and rage; m: = Mann-Whitney test, Parental separation anxiety scale _PSAS_, paediatric anaesthesia emergence delirium _PAED, paediatric sedation agitation scale _PSAS_.

The present study showed that group of dexmedetomidine intranasally had significant reduction in HR compared to intranasal midazolam with p value = 0.023 at 30 mins, and also significant reduction in arterial blood pressure with p value < 0.001 at 30 mins. This could be justified by action of dexmedetomidine on increasing vagal tone and decreasing circulating catecholamine levels and sympathetic flow[10].

Similarly, Saad et al.[1], has recorded that no significant difference between both groups after 10 and 20 min of intranasal drugs administration. But, after 30 min, the HR and BP were significantly lower in dexmedetomidine group than midazolam group. This was also recorded by Abdelmoneim et al.[11], who found significant decrease in mean BP and HR after 30 min from intranasal dexmedetomidine (1 µg/kg), in comparison with intranasal midazolam (0.5 mg/kg).

In this study,onset of sedation is 5.14 ± 1.77 min in Group M compared with 17.49 ± 4.05 min in Group D (early onset in midazolam) (p value < 0.001). Sheta et al.[7], described a similar outcome regarding the onset of sedation as intranasal dexmedetomidine was delayed compared with intranasal midazolam.

Yuen et al.[12], discovered that intranasal dexmedetomidine has a sedative effect after 45-60 minutes, with a peak impact after 90-105 minutes in a healthy population. As stated by Saad et al.[1], the Modified Observer's Assessment of Alertness/Sedation Scale was considerably lower in the midazolam group after 10 and 20 minutes compared to the dexmedetomidine group. However, after 30 minutes, it was considerably lower in the dexmedetomidine group. This demonstrates that midazolam onset of sedation is faster than dexmedetomidine.

In the present study, the patents in dexmedetomidine group were separated more easily from their parents rather than the midazolam group;(p value < 0.001), similarly Ayushi[13] recorded that dexmedetomidine group Parental separation was achieved in 73.3% of patients in comparison to 46.7% in midazolam group (P = 0.035).

Also Darshna et al.[14], noted that children in dexmedetomidine group were acceptably separated from parents than in midazolam group at the time of transferring the patients to operation room, 54% of dexmedetomidine group reached Child Separation Score of 1 in comparison to 40% in midazolam group. These results are in agreement with Ghali et al.[15], who found that the percentages of children in the dexmedetomidine group compared with the midazolam group (78%) vs (63%) achieved child-parents separation score grade 1 (P = 0.029).

Furthermore, children in dexmedetomidine group reached lower agitation score than midazolam group (p value < 0.001). Sheta et al.[7], reported similar results regarding postoperative agitation by reporting a lower percent in children with postoperative agitation in the dexmedetomidine group (agitation score reached 3, 4) significantly compared to midazolam group (11.1% vs. 30.6%) respectively, (P = 0.036). In contrary to Saad et al.[1], they stated that both drugs decreased post-operative agitation, with no statistically significant differences among both groups at 10 and 15 min but statistically significant at 20 and 45 min.

Hesham et al.[16], concurred with our findings, indicating that the PAED scale scores were significantly elevated in the control group compared to the dexmedetomidine and midazolam groups, and that the midazolam group also exhibited significantly higher scores than the dexmedetomidine group. Furthermore, the incidence of emerging delirium was considerably higher in the midazolam and control groups than the dexmedetomidine group.

Evolving Studies on the perioperative use of dexmedetomidine are strengthening the role of dexmedetomidine in preventing postoperative agitation, Ibacache et al.[17], concluded that administration of dexmedetomidine (0.3 µg/kg) after induction of anesthesia decreases the post-sevoflurane agitation in children with insignificant adverse effects.

We observed few adverse effects during the study, and here was no evidence of respiratory depression , apnea or desaturation, which emphasis that the doses used for both drugs are safe and effective and support the findings of other studies.

Conclusion

In children undergoing upper GI endoscopy, premedication with dexmedetomidine at a dose of 1 µg/kg resulted in reasonable sedation, better parent separation, and lower postoperative agitation and delirium compared to intranasal midazolam at 0.2 mg/kg. However, dexmedetomidine had a delayed onset of action.

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