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Midazolam por Via Oral como Medicação Pré-Anestésica em Crianças e Adolescentes com Paralisia Cerebral. Estudo Comparativo das Variações do Índice Bispectral*

Oral Midazolam as Pre-Anesthetic Medication in Children and Teenagers with Cerebral Palsy. A Comparative Study on the Variations of the Bispectral Index

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RESUMO

Costa VV, Torres RVSD, Arci ECP, Saraiva RA — Midazolam por Via Oral como Medicação Pré-Anestésica em Crianças e Adolescentes com Paralisia Cerebral. Estudo Comparativo das Variações do Índice Bispectral.

JUSTIFICATIVA E OBJETIVOS: *O midazolam é um derivado benzodiazepínico com ação hipnótica e muito utilizado como medicação pré-anestésica em anestesia pediátrica. As crianças com paralisia cerebral (PC) também se beneficiam do uso do midazolam, mas seus efeitos são ainda desconhecidos sobre esse grupo de pacientes que apresentam uma série de particularidades, com alterações inclusive no local de ação do midazolam. O objetivo do estudo foi avaliar a ação do midazolam utilizado como medicação pré-anestésica sobre o índice bispectral (EEG-BIS) dos pacientes com paralisia cerebral.*

MÉTODO: *Foram avaliados dois grupos de pacientes: um com diagnóstico de PC e outro sem doença do sistema nervoso central (SNC) e periférico. Foram registrados valores de EEG-BIS na enfermaria na véspera da operação e no dia da operação, 40 minutos depois da administração de 0,6 mg.kg^{-1} de midazolam via oral. Foram excluídos pacientes com história de reação paradoxal ao midazolam e pacientes do grupo-controle que estivessem em uso de outra medicação.*

RESULTADOS: *Foram estudados 77 pacientes de ambos os sexos, entre 4 e 18 anos de idade. Não houve diferença entre os valores de EEG-BIS basal entre os grupos estudados. Após o uso do midazolam houve diminuição dos valores do EEG-BIS nos dois grupos estudados, com diferença estatística significativa em cada grupo. Na comparação entre grupos não houve diferença estatística.*

CONCLUSÕES: *O midazolam administrado como medicação pré-anestésica na dose de 0,6 mg.kg^{-1} diminui os valores basais do EEG-BIS sem caracterizar hipnose e sem diferença estatística nos grupos estudados.*

Unitermos: CIRURGIA, Pediátrica; MEDICAÇÃO PRÉ-ANESTÉSICA: midazolam; MONITORIZAÇÃO: índice bispectral.

SUMMARY

Costa VV, Torres RVSD, Arci ECP, Saraiva RA — Oral Midazolam as Pre-Anesthetic Medication in Children and Teenagers with Cerebral Palsy. A comparative Study on the Variations of the Bispectral Index.

BACKGROUND AND OBJECTIVES: *Midazolam is a benzodiazepine with hypnotic action widely used as pre-anesthetic medication in pediatric anesthesia. Children with cerebral palsy (CP) also benefit from the use of midazolam, but its effects on this group of patients, who present several particularities, including changes at the site of action of midazolam, are still unknown. The objective of this study was to evaluate the effects of midazolam, when used as pre-anesthetic medication, on the bispectral index (EEG-BIS) of patients with cerebral palsy.*

METHODS: *Two groups of patients were evaluated: one group with the diagnosis of CP and the other without central and peripheral nervous system disorders. The EEG-BIS was recorded in the room, the day before the surgery, and at the day of the surgery, 40 minutes after the administration of 0.6 mg.kg^{-1} of oral midazolam. Patients with a history of paradoxal reaction to midazolam as well as patients in the control group who were using other medications were excluded.*

RESULTS: *Seventy-seven patients of both genders, 4 to 18 years old, participated in this study. Differences in EEG-BIS between both groups were not detected. After the use of midazolam EEG-BIS decreased in both groups with a statistically significant difference in each group. Statistically significant intergroup differences were not observed.*

CONCLUSIONS: *Midazolam, used as pre-anesthetic medication, at a dose of 0.6 mg.kg^{-1}, reduced basal EEG-BIS without characterizing hypnosis and without statistically significant differences between the study groups.*

Key Words: MONITORING: bispectral index; PRE-ANESTHETIC MEDICATION: midazolam; SURGERY: pediatric.

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estudo, não foi encontrada nenhuma referência que cite que o monitor de EEG-BIS sofra influência dessa variável.
Em relação ao estado físico, a maior parte dos pacientes com diagnóstico de PC apresenta outras doenças associadas, resultando na classificação de estado físico II (ASA) para 77,3% do grupo com PC, diferente do grupo sem doença do SNC e periférico.
É difícil a comparação com outros estudos similares porque a paralisia cerebral, diante das variedades de formas clínicas da doença, permanece pouco estudada. Não foi encontrado nenhum estudo com método semelhante que permitisse a comparação. O que gostaríamos de registrar é que os pacientes com paralisia cerebral podem se beneficiar do uso do midazolam via oral como medicação pré-anestésica, com o objetivo de diminuir a ansiedade pré-operatória, sem que a dose empregada possa levar ao grau profundo de hipnose, o que acarretaria risco adicional para esses pacientes. Houve diminuição dos valores do EEG-BIS após o uso do midazolam via oral, que não diferiu do obtido nos pacientes do grupo-controle e que configurou nível leve de sedação [10]. Em relação aos pacientes do grupo-controle, já foi descrito em estudo anterior que a dose de 0,8 $mg.kg^{-1}$ de midazolam via oral como medicação pré-anestésica não interferiu nos valores médios basais do EEG-BIS nos pacientes sem doenças do SNC e periférico [12].
O presente estudo tem algumas limitações, como o fato de não ser aleatório, incluir todas as formas clínicas da paralisia cerebral, o que pode levar a uma variabilidade muito grande dos valores médios basais do EEG-BIS, e não ter sido utilizada escala de sedação para avaliação do efeito clínico do midazolam. O próprio método do estudo favoreceu essas limitações. Por incluir um grupo de pacientes com determinada doença não foi possível formar os grupos de forma aleatória. Foram incluídas todas as formas clínicas da PC porque elas fazem parte do dia-a-dia e o objetivo era avaliar o comportamento dos pacientes com PC sem distinção de forma clínica. Não foi empregada escala de sedação porque, além de não ser o objetivo do estudo, teria sido inviável sua aplicação em pacientes com comprometimento cognitivo ou retardo mental.
Nas condições do estudo foi possível concluir que o midazolam por via oral, utilizado na dose de 0,6 $mg.kg^{-1}$, como medicação pré-anestésica, em pacientes com PC, agiu diminuindo os valores médios basais do EEG-BIS para níveis de sedação leve que não são compatíveis com os níveis encontrados no estado de hipnose.

Oral Midazolam as Pre-Anesthetic Medication in Children and Teenagers with Cerebral Palsy. A Comparative Study on the Variations of the Bispectral Index

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INTRODUCTION

Midazolam is a benzodiazepine and it is currently the tranquilizer used more often as pre-anesthetic medication in pediatric anesthesia [1]. In the last 20 years an increase in its use, compared to other drugs used as pre-anesthetic medication, has been reported [2].
Preoperative anxiety affects most patients and some factors contribute for this: separation from the family, postoperative pain, disability, and loss of independence. Studies have demonstrated that midazolam has several benefits and, among them, we could mention a reduction in preoperative anxiety, better cooperation, and it has a short half-life and good absorption after oral administration [3].
Cerebral palsy (CP) is a non-progressive posture and movement disorder secondary to a static lesion of the developing brain [4]. The incidence of CP is approximately 2:1,000 live born in developing nations.
It frequently requires surgical interventions to correct deformities or for complementary exams, which, in those patients, are done under general anesthesia or sedation. In those situations, the knowledge of the particularities related to patients with CP, who often require special care due to their many incapacities and associated diseases, is important. The disruption of several organ systems associated with the brain lesion, such as gastroesophageal reflux, changes in the respiratory system, joint deformities, seizures, behavioral changes, and mental retardation make those patients a special case [5,6]. However, one should not forget that they have feelings and emotions and that their degree of understanding can be greater than one can imagine [6,7]. Therefore, they should be treated like any other child in the pre-anesthetic evaluation, and a multidisciplinary approach involving the surgical, nurse, psychology, and anesthesia teams is necessary. The administration of pre-anesthetic medication is also necessary in most patients. Since midazolam is widely used throughout the world[1], it is also frequently used in patients with CP, but its effects in those patients are not fully known.
Cerebral palsy is often associated with behavioral and communications changes. Approximately two thirds of CP patients present mental retardation, which, in 50% of them is severe [5]. Even patients who are not mentally retarded present attention deficit and behavioral changes, hindering

the use of a clinical scale to evaluate the degree of sedation. Consequently, a means to evaluate objectively the degree of sedation, which is currently available, is very useful in those cases. This study was based on those principles, and its objective was to evaluate the effects of oral midazolam, as a pre-anesthetic medication, on the electroencephalogram (EEG), expressed by the bispectral index (BIS), in patients with CP.

METHODS

The study was approved by the Ethics and Research Committee of the institution. Two groups of patients were evaluated prospectively - Group 1: patients with the clinical diagnosis of CP according to the criteria of the Rede Sarah de Hospitais de Reabilitação [7]. Group 2: patients without central or peripheral nervous system disorders (patients without CP). Patients and/or guardians signed the informed consent.

All patients were to undergo orthopedic or repair plastic surgery and were evaluated by an anesthesiologist at the anesthesia outpatient clinic, approximately 10 days before surgery, and in the ward the day before the surgery. The day before the surgery, with the patient awake and resting in dorsal decubitus, the electrodes followed by the EEG-BIS monitor were installed according to the International 10-20 System of the International Society of Clinical Neurophysiology for electrode placement [8]. Patients were asked to close their eyes and within a 10-minute interval and with at least 50% of signal quality (SQI) the values of the EEG-BIS were determined. The values obtained during this time were recorded on a standard protocol card and later the mean value, which was used as the baseline EEG-BIS, was calculated.

On the day of the surgery, patients received 0.6 $mg.kg^{-1}$ of oral midazolam 40 minutes before the surgery. Upon arrival at the anesthetic induction room, patients were monitored with non-invasive blood pressure, continuous electrocardiogram (ECG), peripheral hemoglobin saturation (SpO_2) and, afterwards, with the specific monitoring of the EEG-BIS. The EEG-BIS was measured the same way as the day before to compare the mean baseline level to the mean level after midazolam in each group and then between both groups, i.e., the CP and the control groups.

Considering the cognitive disorder or mental retardation common in patients with CP, and since it was not the objective of the study, a clinical scale to evaluate the degree of sedation was not used.

As a matter of convenience, all patients scheduled for orthopedic and plastic repair surgeries of the lower limbs from January 2005 to February 2006 were enrolled in this study.

Patients younger than 4 years and older than 18 years, with a history of paradoxal reaction to midazolam, non-cooperative patients, and patients in the control group who were on any other medication were excluded.

After the initial evaluation, the CP Group was further divided in five subgroups, according to the degree of motor compromise, to determine whether the EEG-BIS showed a difference among the subgroups.

Statistical analysis consisted on descriptive and exploratory analysis of the data. The Chi-square test for categorical parameters and the *t* test for continuous parameters were used for the demographic data, considering a $p \leq 0.05$ significant. The paired t test was used to evaluate the intragroup basal and post-midazolam EEG-BIS.

RESULTS

Seventy-seven patients, ages four to 18 years participated in this study; 44 had a diagnosis of CP and 33 did not have disorders of the central and peripheral nervous system.

One patient in each group was excluded for lack of cooperation during the determination of the EEG-BIS in the ward.

In the CP Group, all clinical forms of cerebral palsy were included and 31 (70%) patients in this group had mental retardation or cognitive deficit (Table I).

All patients were calm upon arrival to the anesthetic induction room and allowed the specific monitoring with EEG-BIS, and cases of CNS, cardiovascular, and respiratory depression were not observed.

Groups did not show statistical differences in age (Table II).

Males predominated in the CP Group and female patients in the control group (Table II).

As for the physical status (ASA), the majority of the patients in the CP Group was classified as ASA II, while in the control

Table I – Clinical Forms of Cerebral Palsy That Were Included in the Study

Clinical Forms	n	%
Mild spastic diplegia	14	31.8
Moderate spastic diplegia	5	11.4
Mild mixed diplegia	1	2.3
Moderate mixed diplegia	1	2.3
Mild spastic hemiplegia	7	15.9
Moderate spastic hemiplegia	2	4.5
Mild spastic triplegia	1	2.3
Moderate spastic triplegia	2	4.5
Severe spastic quadriplegia	3	6.8
Mild mixed quadriplegia	1	2.3
Moderate mixed quadriplegia	2	4.5
Severe mixed quadriplegia	4	9.1
Monoplegia	1	2.3
Total	44	100.0

n = number of patients

Table II – Demographic Data

Parameters	CP (n = 44)	No CP (n = 33)	p **
Age (years)*	9.7 ± 3.7	11.0 ± 3.0	0.091
Weight (kg)*	29.1 ± 12.1	41.3 ± 16.5	< 0.001
Physical status**			< 0.001
ASA I	7 (15.9%)	21 (63.6%)	
ASA II	34 (77.3%)	12 (36.4%)	
ASA III	3 (6.8%)	0 (0%)	
Gender			
Female	16 (36.4%)	20 (60.6%)	
Male	28 (63.6%)	13 (39.4%)	

*Results expressed as Mean ± SD.
** *t* test for means and Chi-square test for proportions
CP = cerebral palsy; No CP = absence of central and peripheral nervous system diseases; n = number of patients.

Table III – Descriptive Analysis of EEG-BIS Values

	CP (n = 44)		No CP (n = 33)	
Basal EEG-BIS *	94. 9 ± 7.8	97**	96.9 ± 1.0	97**
Post EEG-BIS *	87.0 ± 1.4	91**	91.3 ± 7.5	94**

*Results expressed as Mean ± SD.
** Median.
Basal = before the administration of midazolam; Post = 40 minutes after the administration of midazolam.
CP = cerebral palsy; No CP = absence of central and peripheral nervous system diseases; n = number of patients.

Group most patients were classified as ASA I, and this difference was statistically significant ($p < 0.001$) (Table II).
Both groups differ considerable regarding their weight; the CP Group had lower mean weight than patients in the Control Group ($p < 0.001$) (Table II).
There was a significant correlation ($p < 0.05$) between weight and the EEG-BIS after the administration of midazolam in both groups ($R_{cp} = 0.34$; $R_c = 0.37$).
The mean baseline EEG-BIS was 95.24 in the CP Group and 96.38 in the control Group, but this difference was not statistically significant (Table III).
The mean EEG-BIS after the administration of oral midazolam was 87.02 in the CP Group and 91.27 in the Control Group, which was lower than mean baseline values in both groups, and this difference in each group was statistically significant ($p = 0.00$) (Table III).
After the administration of oral midazolam, EEG-BIS did not show statistically significant differences between both groups.
Patients with CP were subdivided clinically according to the degree of motor involvement in monoplegic, hemiplegic, diplegic, triplegic, and quadriplegic. Mean EEG-BIS values were not statistically different before and after the administration of midazolam, i.e., the reduction in EEG-BIS after the administration of midazolam was not greater in any clinical type ($p = 0.425$).

DISCUSSION

Two groups of patients, one with CP and the other without central or peripheral nervous system disorders participated in this study.
Analysis of the results demonstrated that midazolam, used as pre-anesthetic medication, promoted a reduction in EEG-BIS in both groups. Mean basal EEG-BIS in both groups were similar to that found in other study [9], without differences between the study groups. There was a significant reduction in mean EEG-BIS 40 minutes after the administration of oral midazolam, 0.6 $mg.kg^{-1}$, in both groups, but to a level that did not characterize clinical hypnosis[10]. It has been described in the literature that EEG-BIS above 70 is compatible with levels of mild sedation and not with levels of general anesthesia or hypnosis [10]. After the administration of midazolam, although patients with cerebral palsy showed a tendency for greater reduction of the EEG-BIS, this reduction was not statistically different from that seen in the control group.
Another study evaluated the effects of midazolam administered as pre-anesthetic medication (oral) in children without

central and peripheral nervous system disorders. That study used the dose of 0.5 mg.kg^{-1} of midazolam, which is slightly lower than the dose used in the present study. Mean EEG-BIS in that study after the administration of midazolam was 96, which is higher than the results of the present study (87) [11]. Mean basal EEG-BIS was not recorded. Evaluating the results of both studies, we believe that the reduction in EEG-BIS after the administration of oral midazolam is dose-dependent but, in the doses used in the present study, the EEG-BIS did not reach levels that could characterize hypnosis [10].

Both groups were similar regarding age, but their weight differed, which is a consequence of the baseline disorder. Another study stated that children with CP have associated gastrointestinal disorders that can lead to malnutrition [5]. Many of those patients can also present chewing and swallowing difficulties, favoring malnutrition and low weight [5]. When compared to patients in the same age group without CP, the weight is lower in patients with CP, especially those with more severe clinical forms of the disease who have muscular atrophy secondary to absence of ambulation. The present study included all clinical forms of CP, including severe quadriplegia (patients with motor disruption affecting all four limbs and without a pattern of ambulation) that frequently have associated disorders, such as gastroesophageal reflux, and nutritional and swallowing disorders [5]. Those factors can explain the weight difference detected between the study groups. The correlation between the weight of the patients and the EEG-BIS after the administration of midazolam reinforces the importance of the weight to correct the doses of drugs used in anesthesia, what was done in the present study.

The predominance of male gender in the CP Group in contrast to the female preponderance in the Control Group was a random occurrence, since patients were included in the study as the requests of surgical interventions were made by the attending physician independently of the gender. In the review of the literature done for this study we did not find any references indicating that the EEG-BIS monitor is influenced by this parameter.

As for the physical status, most patients in the CP Group had associated diseases, resulting in the classification II (ASA) for 77.3%, which differed from the Control Group.

Comparison with similar studies is difficult since cerebral palsy, due to the variations of the clinical types of this disorder, has not been extensively studied. We did not find any studies with similar methodology to compare with the present study. It is important to mention that patients with cerebral palsy can benefit by taking oral midazolam as pre-anesthetic medication to decrease preoperative anxiety without a high degree of hypnosis, which could represent an additional risk in those patients. EEG-BIS parameters decreased after the administration of oral midazolam; this effect was not different from that observed in the Control Group, characterizing mild sedation [10]. As for patients in the control Group, it has been described that 0.8 mg.kg^{-1} of oral midazolam , used as pre-anesthetic medication, did not interfere with basal EEG-BIS in patients without central and peripheral nervous systems disorders [12].

The present study has some limitations: it is not randomized, included all clinical forms of cerebral palsy, what can result in accentuated variability of basal EEG-BIS, and a sedation scale was not used to evaluate the clinical effects of midazolam. The study method favored those limitations. Since it included a group of patients with a specific disease, it was not possible to form randomized groups. All clinical forms of CP were included because they are part of daily practice and the objective of the study was to evaluate the behavior of CP patients regardless of the clinical type. A sedation scale was not used because, besides not being the objective of the study, its application to patients with severe cognitive deficit or mental retardation would have been impossible.

Under the conditions of the present study, it is possible to conclude that oral midazolam, 0.6 mg.kg^{-1}, used as pre-anesthetic medication in patients with CP decreases EEG-BIS to the level of mild sedation compatible with levels seen in the state of hypnosis.

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RESUMEN

Costa VV, Torres RVSD, Arci ECP, Saraiva RA — Midazolam por Vía Oral como Medicación Preanestésica en Niños y Adolescentes con Parálisis Cerebral. Estudio Comparativo de las Variaciones del Índice Bispectral.

JUSTIFICATIVA Y OBJETIVOS: *El midazolam es un derivado benzodiazepínico con acción hipnótica y muy utilizado como medicación preanestésica en anestesia pediátrica. Los niños con parálisis cerebral (PC) también se benefician del uso del midazolam, pero sus efectos todavía se desconocen sobre ese grupo de pacientes que presentan una serie de particularidades, con alteraciones inclusive en la región de la acción del midazolam. El objetivo del estudio fue evaluar la acción del midazolam utilizado como medicación preanestésica sobre el índice bispectral (EEG-BIS) de los pacientes con parálisis cerebral.*

MÉTODO: *Se evaluaron dos grupos de pacientes: uno con diagnóstico de PC y el otro sin enfermedad del sistema nervioso central (SNC) y periférico. Se registraron valores de EEG-BIS en la enfermería en la víspera de la operación y el día de la operación, 40 minutos después de la administración de 0,6 mg.kg-1 de midazolam por vía oral. Quedaron excluidos pacientes con historial de reacción paradoxal al midazolam y pacientes del grupo control que estuviesen usando otra medicación.*

RESULTADOS: *Se estudiaron 77 pacientes de ambos sexos, entre 4 y 18 años de edad. No hubo diferencia entre los valores de EEG-BIS basal entre los grupos estudiados. Después del uso del midazolam hubo una reducción de los valores del EEG-BIS en los dos grupos estudiados, con diferencia estadística significativa en cada grupo. En la comparación entre los grupos no hubo diferencia estadística.*

CONCLUSIONES: *El midazolam administrado como medicación preanestésica en la dosis de 0,6 mg.kg^{-1} redujo los valores basales del EEG-BIS sin caracterizar la hipnosis y sin diferencia estadística en los grupos estudiados.*