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# Premedication with midazolam in low-risk surgery in children does not reduce postoperative delirium. Prospective cohort study

*La premedicación con midazolam en cirugías de bajo riesgo quirúrgico en niños no reduce el delirio posoperatorio. Estudio de cohorte prospectivo*

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## What do we know about this topic?

- Pediatric emergency delirium is one of the most frequent and feared anesthetic complications, both by the anesthetic team and by the patient and their family.
- The use of midazolam in children for the prevention of the occurrence of delirium presents controversial evidence.

## What new knowledge does this study contribute with?

- The incidence of delirium continues to be important in the Colombian pediatric population and is close to 14%.
- The use of preoperative midazolam is not associated with a reduction in the incidence of delirium in low-risk surgeries in children.

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## Abstract

**Introduction:** Pediatric postoperative delirium is a frequent complication for which preventive pharmacological measures have been suggested. The use of midazolam as a prophylactic strategy has not yet been thoroughly assessed. Notwithstanding the fact that it is used in pediatric presurgical separation anxiety, its role in delirium is yet to be established.

**Objective:** To quantify the incidence of pediatric postoperative delirium in patients undergoing low risk surgical interventions, exposed to oral midazolam-based premedication and to explore the protective and risk factors associated with the development of delirium.

**Methods:** Prospective, analytical observational study with a cohort design. Children were conveniently selected in accordance with the daily list of surgical procedures in the operating rooms. The inclusion criteria were children between 2 and 10 years old, ASA I-II, undergoing low risk surgeries. Concurrent and longitudinal follow-up was then conducted upon admission to the post-anesthesia care unit (PACU) for the first hour.

**Results:** A total of 518 children were included. The overall incidence of delirium was 14.4% (95% CI: 11.4%-17.5%). In the subgroup exposed to midazolam, 178 children were analyzed, with an incidence of delirium of 16.2% (95% CI of 10,8%-21,7). These patients exhibited a higher tendency to delirium with the use of sevoflurane or fentanyl, and/or when presenting with severe postoperative pain. Patients exposed to propofol and/or remifentanyl showed lower incidences.

**Conclusions:** No reduction in the incidence of emergency pediatric delirium associated with the use of pre-surgical oral midazolam in low risk surgical procedures. Prospective controlled trials and additional research are required to study the effectiveness and safety of this intervention.

**Keywords:** Delirium; Emergency delirium; Pediatrics; Midazolam; Postoperative pain; Anesthesiology.

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## Resumen

**Introducción:** El delirio pediátrico posoperatorio es una complicación frecuente para la cual se han sugerido medidas farmacológicas de prevención. El uso de midazolam como estrategia profiláctica aún no ha sido suficientemente evaluado. A pesar de que se emplea para la ansiedad de separación pediátrica prequirúrgica, su papel en delirio aún no se ha establecido.

**Objetivo:** Cuantificar la incidencia de delirio pediátrico posoperatorio en pacientes sometidos a cirugías de bajo riesgo quirúrgico, expuestos a premedicación basada en midazolam oral y adicionalmente, explorar los factores protectores y de riesgo asociados a la ocurrencia.

**Materiales y métodos:** Estudio observacional analítico prospectivo con un diseño de cohorte. Se seleccionaron niños por conveniencia de acuerdo con la lista quirúrgica diaria en salas de cirugía. Como criterios de inclusión se tomaron sujetos entre 2 y 10 años de edad, ASA I-II, sometidos a cirugías de bajo riesgo quirúrgico. Posteriormente se realizó seguimiento concurrente y longitudinal al ingreso a la unidad de recuperación posanestésica (UCPA) durante la primera hora de estancia.

**Resultados:** Se incluyeron 518 niños. La incidencia global de delirio fue del 14,4 % (IC 95 %;11,4 %-17,5 %). En el subgrupo expuesto a midazolam se analizaron 178 niños, quienes presentaron una incidencia de delirio del 16,2 % (IC 95 %;10,8 %-21,7 %). Estos pacientes presentaron una mayor tendencia a delirio con el uso de sevoflurano o fentanilo, y/o cuando presentaron dolor severo posoperatorio. Pacientes con exposición a propofol y/o remifentanilo exhibieron incidencias inferiores.

**Conclusiones:** No se encontró una reducción en la incidencia de delirio pediátrico de emergencia asociada al empleo de midazolam oral prequirúrgico en cirugías de bajo riesgo. Se requieren estudios prospectivos controlados e investigación adicional para el estudio de la efectividad y seguridad de esta intervención.

**Palabras clave:** Delirio; Delirio del despertar; Pediatría; Midazolam; Dolor posoperatorio; Anestesiología.

## INTRODUCTION

Postoperative delirium, emergence delirium (awakening delirium) and post-anesthesia arousal are terms indistinctively used to refer to a number of disorders observed in children during the phase of recovery from general anesthesia. In accordance with the description by Sikich and Lerman, this phenomenon should be seen as “a disturbance in a child’s awareness of and attention to his/her environment, with disorientation and perceptual alterations including hypersensitivity to stimuli and hyperactive motor behavior in the immediate post-anesthesia period”.<sup>(1)</sup> This definition is not applicable to delirium in critical conditions (intensive care), neither to delirium outside of the operating room. Such phenomena and scenarios are beyond the scope of this study.

Cases of post-operative delirium heighten the anxiety of caregivers and medical personnel. In fact, patients often inflict self-injury, remove their drains or catheters and hinder the surgical and anesthetic outcomes, which represent a risk factor for the development of complications.<sup>(2)</sup> The scientific community has developed guidelines and protocols

based on evidence and expert experience for timely prevention and/or treatment; however, its etiology and pathophysiology remain unclear and solid data are still missing to support adequate prophylaxis and management.<sup>(3)</sup> While the literature contributes with different knowledge, the controversy and disagreement exceeds the agreement reached on this matter.

In accordance with the Guidelines on post-operative delirium of the European Society of Anesthesiology published in 2017<sup>(4)</sup>, the prevalence of this condition worldwide ranges between 4 and 80 % (depending on the article considered); however, there is significant lack of knowledge about its prevalence in South America. It was only until 2018 when the study by González et al. described an incidence of 13.2 %, in the Colombian population between 2 and 10 years old, during the postoperative period of low risk surgery.<sup>(5)</sup> This correlates with the statistical data in contemporary articles following the validation studies of the PAEDS scale which were based both on healthcare requirements and investigational criteria in the field. A case in point is the study by Voepel-Lewis.<sup>(6)</sup>

Pursuant to this information and the need to avoid such outcome,

pharmacological and non-pharmacological prevention strategies have been developed. One of them is the inclusion of midazolam indicated as a potent protective factor in pediatric population<sup>(4,7-9)</sup>; however, this statement has been questioned by several authors.<sup>(10-14)</sup> In a previous study by this same research group, an apparent positive effect was described in patients receiving IV midazolam during the administration of anesthesia.<sup>(5)</sup>

The purpose of this study was to establish the incidence of postoperative pediatric delirium in children between 2 and 10 years old, undergoing low-risk surgery under general anesthesia. Additionally, to describe the incidence of delirium and associated factors in subjects receiving oral midazolam as a premedication on the day of the procedure for managing separation anxiety.

## METHODS

Prospective cohort analytical observational study. Children between 2 and 10 years old, classified as ASA-PS I or II were included (Physical Status Classification of the American Society of Anesthesiology),

undergoing low risk surgical procedures under general anesthesia. Based on the study published by González et al. in 2018 (5), which established a prevalence of emergence delirium of 13.2 % in the pediatric population not exposed to midazolam, meeting similar selection criteria to those herein adopted and with a relative hypothetical risk of at least 2.3 and an exposed/non-exposed ratio of 2.0 with 80% power and a confidence of 95 %, a cohort of at least 507 records was estimated (169 of them under midazolam exposure and 338 records of patients who did not receive the drug). Patients with preoperative neurological sequelae and patients transferred to the intensive pediatric care unit were excluded.

The selection criteria were assessed at admission to the post-anesthesia care unit (PACU) and then concurrent and longitudinal follow-up was conducted, in addition to the ongoing monitoring of the institutional surgical healthcare team. The diagnostic parameter for emergence delirium was the PAEDS scale (Pediatric Anesthesia Emergence Delirium Scale). (1) Additionally, the CHEOPS scale (Children's Hospital of Eastern Ontario Pain Scale) (15) was used to establish the presence of uncontrolled acute pain. The data collection form also included the Aldrete scores (16), the use of medication for delirium control and pain. The measurements were recorded from the time of admission to the PACU and every 20 minutes for the first hour of follow-up. "Global" delirium and the presence of uncontrolled acute "global" pain were estimated based on incident cases during the first hour, as well as the instances of delirium and pain at 0, 20, 40 and 60 minutes. Similar measurements were taken from the subgroup exposed to oral midazolam as premedication.

The data base was complemented with the demographic information (weight, age and gender), presurgical clinical variables (i.e., comorbidities) and surgical information (such as the type of procedure, surgical times and anesthetic agents, induction and maintenance of anesthesia,

inter alia). Finally, safety data were recorded such as anesthetic and surgical complications.

The research protocol was assessed and approved by the research and ethics committees of Fundación Universitaria de Ciencias de la Salud (FUCS), Bogotá D.C. and the Fundación Hospital Infantil Universitario de San José, Bogotá, D.C. (Record number 077 of April 20, 2017).

## STATISTICAL ANALYSIS

The information was recorded in an excel database (Version: 19, 2018, Microsoft Inc). Crossed validation was done both when recording the data in the collection forms and when uploading the information to the spread sheet, by the data collection team and one of the study investigators. The qualitative nominal or ordinal variables were presented in absolute frequencies and in percentages. The quantitative normal distribution variables were shown as means and standard deviation, while the quantitative distribution variables different from the normal were reported as medians and interquartile 25 % - 75 % ranges. The Kolmogorov-Smirnov test was used to check for normality.

Global delirium and uncontrolled severe pain were estimated based on the incident cases during the first hour of follow-up (incident cases/exposed population). Similarly, the incidence of delirium and pain at 0, 20, 40 and 60 minutes were estimated. The intensity of delirium was also assessed by classifying the PAEDS scores into three levels (from 10 to 12, from 13 to 16, and from 17 to 20) and were cross-referenced against pain. Stratified incidences were established in accordance with the known risk factors: age less than 5 years old, head and neck surgery, ENT surgery, exposure to halogenated agents and controlled pain. Likewise, stratified incidences were established in accordance with the known protective factors: analgesics, intravenous inducers and regional anesthesia/analgesia. The

same calculations were made for the subgroup of patients premedicated with midazolam.

For delirium and pain outcomes a bi-variate analysis was conducted. Hypotheses contrasts were conducted to compare dichotomous nominal variables using statistical Chiz, whilst the U-Mann Whitney's test was used for non-parametric variables. The safety parameters used were time to reach an Aldrete score of 10, the percentage of patients with an Aldrete score below 7 at admission, and complications. The statistical calculations were conducted using the SPSS 22 software with a statistical significance established as values below 5 % ( $p < 0.05$ ).

## RESULTS

A total of 518 patients were included in the study; 178 were children exposed to oral midazolam as premedication. The demographics and the clinical characteristics of the population are depicted in Table 1. There was a predominance of males (70.7%), ASA I (91.7%), surgical and anesthesia times (average) < 90 minutes, and in general, maximum fasting of 12 hours. The most frequent surgical interventions were Urology, Orthopedics, Pediatric Surgery and ENT (91.5 % in the group without midazolam and 90.8 % in the midazolam group).

The global incidence of delirium was 14.4 % (95 % CI: 11.4 %-17.5 %) (Table 2), being higher at minute 0 (12.9 %) and lower at minutes 20 and 40 (4.2 % and 0.8 %, respectively). Similar values were found in the subgroup exposed to midazolam (global incidence of 16.2 % [95 % CI: 10.8 %-21.7 %]), being higher at minute 0 (16.3 %) and lower at minutes 20 and 40 (1.7 % and 0.0 %, respectively).

When stratifying the intensity of delirium in accordance with the PAEDS scores, 76.1 % (51 of 67) of the cases in minute 0 had values between 10 and 12, while 81.8 % (18 of 22) of the cases in minute 20 exhibited values between 10 and 12

**Table 1.** Demographic and clinical characteristics of the cohort (n = 518).

Variables	Overall values (n = 518)	Non exposed to midazolam (n = 340)	Exposed to midazolam (n = 178)	P
Age (Years)	5 (3-7)	5 (3-7)	5 (3-7)	0.819
Weight (Kg)	20 (15-25)	19 (15-24)	20 (15-25)	0.252
Sex (Male)	366 (70.7 %)	245 (72.1 %)	121 (68 %)	0.193
ASA 1 vs. ASA 2 (%)	475 (91.7 %) vs. 43 (8.3 %)	308 (90.6 %) vs. 32 (9.4 %)	167 (93.8 %) vs. 11 (6.2 %)	0.135
Comorbidities (%)	36 (6.9 %)	25 (7.4 %)	11 (6.2 %)	0.382
Fasting (hours)	8 (8-12)	8 (8-10)	8 (8-12)	0.017*
>12 hours	77 (14.9 %)	59 (17.4 %)	18 (10.1 %)	
Anesthesia time (minutes)	60 (45-90)	60 (40-80)	70 (45-100)	<0.001*
Surgical time (minutes)	45 (30-70)	40 (25-60)	50 (30-80)	<0.001*
Surgical specialties. n (%)				0.027*
- Urology	203 (39.2 %)	128 (37.6 %)	75 (42.1 %)	
- Orthopedics	70 (13.5 %)	43 (12.6 %)	27 (15.2 %)	
- Pediatric surgery	129 (24.9 %)	98 (28.8 %)	31 (17.4 %)	
- ENT	72 (13.9 %)	40 (11.8 %)	32 (18.0 %)	
- Others	44 (8.5 %)	31 (9.1 %)	13 (7.3 %)	

Notes: Figures expressed as medians, ranges 25-75, frequencies and percentages. \*p < 0.05.

ASA: Classification of the American Society of Anesthesia. Source: Authors.

**Table 2.** Incidence of pediatric postoperative delirium and uncontrolled severe postoperative pain.

Assessment time	Incidence of delirium n (%)	Incidence of delirium. Exposed to midazolam n (%)	Incidence of delirium. Non exposed to midazolam n (%)	p value
Minute 0	75 (14.5 %)	29 (16.3 %)	46 (13.5 %)	0.235
Minute 20	67 (12.9 %)	29 (16.3 %)	38 (11.2 %)	0.067
Minute 40	22 (4.2 %)	3 (1.7 %)	19 (5.6 %)	0.026*
Incidence	4 (0.8 %)	0 (0 %)	4 (1.2 %)	0.184
Assessment time	Incidence of uncontrolled acute pain n (%)	Incidence of uncontrolled acute pain. Exposed to midazolam n (%)	Incidence of uncontrolled acute pain. Non exposed to midazolam n (%)	p value
Minute 0	122 (23.6 %)	36 (20.2 %)	86 (25.3 %)	0.118
Minute 20	93 (18.0 %)	28 (15.7 %)	65 (19.1 %)	0.203
Minute 40	59 (11.4 %)	9 (5.1 %)	50 (14.7 %)	< 0.001*
Minuto 40	20 (3.9 %)	6 (3.4 %)	14 (4.1 %)	0.438

Note: Values shown in frequencies and percentages. Delirium assessment scale: PAEDS (Pediatric Anesthesia Emergence Delirium Scale). Delirium: a score higher or equal to 10 in PAEDS. Scale for assessing acute uncontrolled pain: CHEOPS (Children's Hospital of Eastern Ontario Pain Scale). Uncontrolled acute pain: a score > 6 in CHEOPS. \*p < 0.05. Source: Authors.

(Table 2). With regards to the midazolam-treated subgroup, the stratification of delirium intensity according to the PAEDS ratings was 89.7 % (26 of 29) of the cases at minute 0 showed values between 10 and 12, and 100 % (3 of 3) of the cases at

minute 20 exhibited values between 10 and 12 (Table 2).

The development of delirium varied among the patients presenting with uncontrolled pain (Table 3). The global incidence of delirium in that group was

higher (29.5 % vs. 9.8 %, p < 0.0001). Moreover, patients with uncontrolled pain experienced a higher intensity of delirium: At minute 0, 29.4 % (15 of 51) of the patients with PAEDS between 10 and 12 presented with uncontrolled pain; 66.7 % (8 of 12) of

**Table 3.** Incidence of pediatric postoperative delirium and acute uncontrolled pain among the study patients.

Incidence of delirium	Global			Non exposed to midazolam			Exposed to midazolam		
	Acute uncontrolled pain n (%)	Acute controlled pain n (%)	P	Acute uncontrolled n (%)	Acute controlled n (%)	P	Acute un-controlled pain n (%)	Acute controlled pain n (%)	P
Global	36 (29.5 %)	39 (9.8 %)	< 0.001	26 (30.2 %)	20 (7.9 %)	< 0.001	10 (27.8 %)	19 (13.4 %)	0.038
Minute 0	27 (29.0 %)	40 (9.4 %)	< 0.001	21 (32.3 %)	17 (6.2 %)	< 0.001	6 (21.4 %)	23 (15.3 %)	0.290
Minute 20	13 (22.0 %)	9 (2.0 %)	< 0.001	13 (26.0 %)	6 (2.1 %)	< 0.001	0 (0 %)	3 (1.8 %)	0.855
Minute 40	0 (0 %)	4 (0.8 %)	0.854	0 (0 %)	4 (1.2 %)	0.845	0 (0 %)	0 (0 %)	-

**Notes:** Analysis of the impact of acute uncontrolled pain on the incidence of pediatric postoperative delirium. Acute uncontrolled pain: CHEOPS > 6. Acute controlled pain: CHEOPS less than or equal to 6. CHEOPS: Children's Hospital of Eastern Ontario Pain Scale.

**Source:** Authors.

**Table 4.** Comparison between the incidence of postoperative delirium between categories of type of extubation and Aldrete score.

	Incidence of delirium n (%)	Incidence of delirium. Exposed to midazolam n (%)	Incidence of delirium. Non exposed to midazolam n (%)
Deep extubation vs. awake extubation	16/95 (16.8%) vs. 59/423 (13.9%) p = 0.281	12/26 (46.2%) vs. 17/152 (11.2%) p < 0.0001	4/69 (5.8%) vs. 42/271 (15.5%) p = 0.022
Aldrete < 7 vs. Aldrete 7 or higher	14/42 (33.3%) vs. 61/476 (12.8%) p = 0.001	10/19 (52.6%) vs. 19/159 (11.9%) p < 0.0001	4/23 (17.4%) vs. 42/317 (13.2%) P = 0.379

**Note:** Analysis of the association between Aldrete scores and the incidence of pediatric postoperative delirium, the type of extubation and the rate of pediatric postoperative delirium.

**Source:** Authors.

the patients with PAEDS between 13 and 16 experienced uncontrolled pain, and 100 % (4 of 4) of the individuals with PAEDS scores between 17 and 20 experienced uncontrolled pain. In the case of the subgroup exposed to midazolam, the global incidence of delirium was higher (27.8 % vs. 13.4 %, p = 0.038) (Table 3). Patients with uncontrolled pain showed a higher intensity of delirium: At minute 0, 15.4 % (4 of 26) of the patients with PAEDS between 10 and 12 presented with uncontrolled pain; 50 % (1 of 2) of the subjects with PAEDS between 13 and 16 presented with uncontrolled pain and 100 % (1 of 1) of the subjects with PAEDS scores between 17 and 20 presented with uncontrolled pain.

In general, the patients exhibited an Aldrete score of 8 (8-9) at admission to the PACU, and required 15 minutes in average (8-20 minutes) to reach an Aldrete score of 10. 45.4 % required less than 10 minutes to achieve total recovery. In this case, patients with delirium showed lower scores at admission 8 (8-9), p < 0.001; longer times to achieve an Aldrete score of 10, 20 min (10-25 min), vs. 15 min (5-20 min), p = 0.004, and only 31.1 % of the patients achieved an ideal Aldrete score in less than 10 minutes (vs. 68.7 % without delirium, p = 0.009). Notwithstanding the fact that 6.8 % of the population exhibited an Aldrete score < 7 at admission to the PACU, only 4.3 %

experienced delirium, while 11.7 % of the subjects with Aldrete scores > 7 met the diagnostic criteria for delirium; however, the data did not show any statistically significant differences (Table 4).

Moreover, children in the midazolam-exposed group, exhibited an Aldrete score of 8 (8-9) at admission to the PACU and required 20 minutes in average (10-20 minutes) to reach an Aldrete of 10; furthermore, 28.7 % required less than 10 minutes for complete recovery (Aldrete = 10). The analysis of these scores in the group of patients with delirium showed that in average they exhibited lower scores at admission 8 (6-8), p < 0.0001; longer

times to reach an Aldrete score of 10 (20 min [17.5-40 min], vs. 20 min [10-20 min]),  $p = 0.026$ , and only 11.8 % of them reached the ideal Aldrete in less than 10 minutes. In fact, 10.7 % of the population presented an Aldrete score  $< 7$  at admission to the PACU, and of these 52.6 % experienced delirium, while only 11.9 % of the subjects with an Aldrete score  $> 7$  met the diagnostic criteria for delirium ( $p < 0.0001$ ) (Table 4).

The analysis of the demographic data (such as age less than 5 years old and gender), clinical variables (such as the type of surgery, head and neck surgery, surgical times, anesthesia technique, the type of induction of anesthesia, the anesthesia maintenance strategy and preventive and therapeutic analgesia), resulted in all cases in risk or protective factors discussed in the world literature for emergence pediatric delirium. However, none of these factors exhibited any relevant differences. In contrast, the bivariate global analysis of delirium did not show any protective or risk factors. The analysis of the midazolam exposed subgroup revealed that some of the medications administered intraoperatively were considered protective factors, including the use of propofol ( $p = 0.043$ ), remifentanyl ( $p = 0.001$ ), diclofenac ( $p = 0.006$ ) and desflurane ( $p = 0.042$ ). Moreover, longer surgical times ( $p = 0.014$ ), the use of fentanyl ( $p = 0.009$ ), sevoflurane exposure ( $p = 0.042$ ) and deep plane extubation and then transfer to the PACU under such neurological condition ( $p < 0.0001$ ) were all associated with a higher incidence of delirium. Some known risk or protective factors – of significant interest for the study – such as: age under 5 years old ( $p = 0.478$ ), gender ( $p = 0.111$ ), ASA ( $p = 0.258$ ), fasting ( $p = 0.332$ ), head and neck surgery ( $p = 0.347$ ), dexamethasone ( $p = 0.614$ ) and regional analgesia ( $p = 0.288$ ) did not show any significant differences.

Finally, in the midazolam-treated subgroup, whilst uncontrolled pain was higher among the pediatric and ENT surgery groups ( $p = 0.028$ ), the patients who received halogenated compounds for induction and maintenance ( $p = 0.026$ )

presented a lower incidence. Despite the absence of statistically significant differences in the stratified incidence of pain with regards to the use of regional analgesia, clinically relevant differences were identified (10.7 % vs. 22.0 %,  $p = 0.131$ ). None of the analgesic measures showed any significant difference in the prevention of uncontrolled pain. The analysis of the analgesic effects of tramadol, diclofenac, dipyron, morphine and hydromorphone in the prevention of acute uncontrolled pain, all of these agents showed an average effectiveness of 80.8 % (at minute 0, an efficacy of 85.5 %, at minute 20 an efficacy of 95.1 % and at minute 40 an efficacy of 96.1 %). These data were similar to the overall results with regional analgesia, (efficacy at minute 0 of 89.3 %, at minute 20 of 100 % and at minute 40, 100 %). 3.9 % of the patients (7 of 178) received hydromorphone for pain control, as part of the management of delirium, with 100 % achieving the desired effect (analgesic and/or anti-delirium). Such findings are better than the results in the population with no midazolam exposure; in fact, among the latter, no major benefits were found with regional analgesia (25.3 % vs. 25.3 %,  $p = 0.328$ ). The analysis of the analgesic effects of tramadol, diclofenac, dipyron, morphine and hydromorphone for the prevention of severe acute pain, all of these agents showed an average effectiveness of 74.14 % (at minute 0 an efficacy of 78.46 %, at minute 20 an efficacy of 86.22 %, and at minute 40 an efficacy of 96.1 %). None of the patients experienced any anesthetic or surgical complications.

## DISCUSSION

Postoperative delirium has been described as a condition of disassociation following anesthesia, usually self-limiting and not exceeding 60 minutes but difficult to diagnose because of the multiple associated confounding factors (for instance, acute uncontrolled pain). (1,4) It has been studied and characterized in children over the

past 20 years. For decades, the estimates of its global and stratified prevalence was a pending task and there is still room for improvement by those interested in the area. The current estimates remain unclear because of the confounding variables and limitations of the studies published. (2) A case in point is the variability in the range of incidence reported in the literature (between 10 % and 50 %). (6,14,17)

A potential source of controversy may be the poor knowledge about the standardized diagnostic criteria. In response to this situation, validated scales such as PAEDS (Sikich and Lerman) (1) have been implemented, with a view to diagnosing this subtype of delirium among the pediatric population. Needless to say that the inclusion of this tool significantly improved the identification and intervention of the condition. A previous study published by the authors herein, discussed the general incidence rates of delirium reported in similar age groups undergoing low risk surgeries, and the most consistent global figures resulting from globalization and implementation of scales with a stronger epidemiological significance (5).

This study estimated a 14.48 % incidence of emergence delirium (without midazolam), and of 16.29 % in midazolam premedicated pediatric patients undergoing low-risk surgical procedures. However, this number was higher than the 13.2 % published in the previous 2018 study. (5) Though we must keep in mind that in such project patients failed to receive any preventive measures for emergence delirium, in contrast with the patients in this study. Whilst this data may not preclude the preventive value of oral midazolam as an anti-delirium agent as published by other authors, the benefits claimed in various articles are controversial for the Latin population.

Various authors have claimed that separation anxiety is not only a common event faced by the pediatric anesthesiologist which affects the peace of mind of caregivers and the OR team,

but it is also considered to facilitate postoperative delirium. (4) This is why the guidelines have included and supported midazolam. However, its efficacy has been debated in several analyses. (3,18) Clinical trials have documented a significant reduction in delirium associated with midazolam as a prevention strategy. (7,8) These statistical data are consistent with the impact factors described by Fang et al. in their meta-analysis on the prophylactic use of midazolam (versus placebo), showing a significant protective effect (OR = 0.22, 95 % CI between 0.07 and 0.60). (9). Similarly, Costi et al., described an apparent preventive effect in patients receiving intraoperative IV boluses (RR = 0.57, 95 % CI between 0.41 and 0.81). (10) In contrast, the contemporary literature has claimed an absence of any effect associated with such intervention. In the article by Dahmani et al., their meta-analysis reported no differences in the rates of emergence pediatric delirium despite the use of midazolam. (11) Furthermore, there are no studies on the undesirable side effects of midazolam: restlessness, paradoxical reactions and other negative postoperative behaviors. (12) However, a potential association has been described between the use of midazolam and the occurrence of postoperative delirium. A case in point is the report by Breschan, who identified a higher incidence of postoperative agitation following the administration of high doses of rectal midazolam. However this data is not supported by a significant difference and exhibits definition biases because of failure to include an external broad validity scale to contribute to our existing knowledge about delirium. (13)

In view of the contradictory evidence, it should be noted that the scientific support is weak to endorse this pharmacological approach. Apparently midazolam only improves the conditions at admission to the OR but not the neurological pediatric post-anesthesia outcomes. It is still relevant to conduct more rigorous and internal and external validity studies to reassess such

approach, in a sufficiently comprehensive manner, linked to the analysis of macrodata.

There are numerous and varied risk factors associated with the etiology of delirium; most of them resulting from its eventual occurrence and/or attributed by tradition. However, some of the risk factors analyzed pursuant to a scientific model include preoperative anxiety, exposure to general anesthesia mostly based on the use of volatile anesthetic agents, and the presence of postoperative pain, inter alia.

The origin of this acute neurological dysfunction still lacks a clear identification of its cause. There are contradictory arguments between a non-specific and global cortical-subcortical involvement versus a unique circuitry disconnection syndrome associated with tasks and rest (depending on neural growth and development conditions). (3) Preventive interventions have focused on a timely assessment (in time and space) and on a potential modification of specific risk factors – as those previously mentioned –; hence it is important to understand the adequate monitoring during the first 60 minutes post-anesthesia since almost all of these events develop during this period of time. This study reported the development of emergence delirium within the first 20 minutes upon admission to the PACU in all cases, and a complete resolution within the first hour. The higher incidence of delirium at admission among patients undergoing shorter duration surgeries should also be noted.

One hypothesis that warrants further discussion is the pharmacodynamic effect of multiple simultaneous medications on mental function, in addition to the way in which the brain circuitry recovers control as the various molecules leave their effector sites, discontinuing their clinical effect and allowing for the development of certain phenomena such as delirium. As of this date there is no comprehensive axiom to explain such behavior and to enable a general prediction about the type of awakening. Kuratani (17) in 2008 and Kanaya in 2016(3), independently argued the pro-delirium effect of sevoflurane. The

former conducted a systematic review and a meta-analysis and found a significant increase in the prevalence of pediatric delirium associated with sevoflurane, and hence a strong association with such complication (OR = 2.21 95 % CI: 1.77-2.77). (17) Similarly, Kanaya summarized and analyzed the evidence of the relationship between risk and protective factors, with sevoflurane as a relevant associated factor. (3) There is a higher incidence of delirium in pediatric patients receiving sevoflurane versus patients receiving desflurane (18.6 % vs. 6.7 % p = 0.042). However, other authors (10,18-20) have not found any significant differences between these two agents and the development of delirium.

Such debates support the use of intravenous techniques with a potential protective effect. Specifically propofol has been assessed for the induction and/or prevention of this outcome, based on its well-known modulatory properties of the neuronal activity which apparently do not suppress in an indiscriminate manner the control of the activation and inactivation of the brain, maintaining a synchronized emergence between the level of awareness and the motor and sensory zones in the brain. (14) This report describes a lower incidence of postoperative delirium associated with the use of propofol (14.60 % vs. 35.70 % p = 0.043). Similar data were published in a clinical assay by Wu et al., which found significantly lower PAEDS scores in the population receiving a preventive trans-operative infusion of propofol in patients undergoing general anesthesia with sevoflurane (mean PAEDS score of 5.66±1.74 vs. 9.87±3.15, p < 0.01). (21) Similarly, Chandler et al. found a significantly lower incidence of delirium favoring propofol (38.3 % vs. 14.9 %, p = 0.018) in children between 2 and 6 years old, who were randomly assigned to induction and maintenance using total inhaled sevoflurane versus total intravenous anesthesia for induction and maintenance based on remifentanyl plus propofol. (22) These data have been supported before and after by the meta-analyses by Dahmani

et al. (11) and Fang (9), which identify propofol as a robust protective agent for postoperative delirium.

Various authors have assessed other medications and the most prominent include opioids, alpha-2 agonists (such as dexmedetomidine and clonidine) and ketamine; these medications apparently reduce the risk when used as part of the anesthesia regimen or simply as prophylaxis for delirium. (9) Though previous analyses have shown evidence supporting the role of fentanyl as an agent not associated with delirium, and even with potential preventive characteristics, this report showed a higher incidence of emergence delirium when the patient received doses of fentanyl for the induction of anesthesia. However, we must not forget that part of the population analyzed had been previously exposed to midazolam to control separation anxiety. This finding is consistent with previous literature reports, including a previous study by the same the group that prepared this report. (5) A meta-analysis by Costi et al. (10), described a lower incidence of delirium in patients receiving fentanyl (RR = 0.37, 95 % CI 0.27-0.50). However, this study should be viewed with caution since the same population treated with fentanyl simultaneously received remifentanyl or sufentanyl as infusion analgesic agent for maintenance of balanced anesthesia. Hence, the results may lead to a conditioned external validation. Nevertheless, when analyzing the effect of remifentanyl in that same study (10), when used as a bolus or infusion, a significant preventive effect was observed (RR = 0.50, 95 CI % 0.30-0.85). In this study, a lower incidence of emergence delirium was identified when the patient received remifentanyl for maintenance of anesthesia in the midazolam subgroup. An explanation for this phenomenon may be the synergistic effect of remifentanyl in infusion, which allows for lower doses for maintenance of inhaled anesthetics, resulting in lower exposure to these agents that have shown a higher incidence of delirium as compared to propofol infusions. Although there may

also be an impact of the half-life of strong opioids used in anesthesia which may facilitate or prevent delirium.

Notwithstanding the fragility of the PAEDS scale to establish hypoactive emergence delirium, it is quite surprising that the midazolam subgroup showed a higher incidence of postoperative delirium in patients extubated in a deep plane versus patients undergoing awake extubation (46.2 % vs. 11.2 %,  $p < 0.0001$ ). For many years this procedure has been traditionally suggested to avoid neurological complications and deliver a smooth awakening to the infant. However, the current evidence contradicts this approach and in fact indicates that it may be a potential trigger for delirium. Additional data from this same cohort exposed to midazolam indicate a high incidence in the percentage of patients admitted to the PACU with Aldrete scores below 7 points (52.6 %) versus patients with scores between 7 and 10 (11.2 %). This may be explained based on the high concentration of anesthetic halogenated compounds when pediatric patients are extubated maintaining spontaneous breathing, as compared to propofol. This finding supports the theory that the high concentrations of hypnotic medications may increase the risk of postoperative delirium during awakening. This argument was submitted by Wu et al., reporting higher Aldrete scores and lower rates of delirium in individuals treated with propofol versus a control group. (21) There is yet no clear explanation for this phenomenon; however, it has been suggested that the effect resulting from anesthetic drugs in individuals with specific non-modifiable variables (i.e., age), together with unique environmental conditions, may trigger the development of a non-specific global involvement of the areas of the brain responsible for awareness, attention, cognition and perception, from a traditional approach (23), or result in an inadequate functional reconnection of separate activation systems in the default activation circuit network. (24)

In the understanding that delirium is the result of multiple factors, the

search for causality has led to the consideration of other variables beyond the pharmacological aspect, but which are present during the perioperative period. Hence, pain and uncontrolled acute pain in particular becomes relevant. This report identified a clinical and statistically significant difference in the percentages of global delirium and midazolam-associated delirium, when the patient is simultaneously experiencing pain. A previous study published by the same group of authors described a similar difference in the incidence of pediatric delirium in children between 2 and 10 years old, undergoing low-risk surgery under general anesthesia (19.8 % vs. 11.0 %). (5) Numerous studies argue that pain is a probable key actor that facilitates or causes delirium. (6,25-27). Notwithstanding this claim, there are epidemiological doubts questioning the administration of scales of similar domains to establish different clinical presentations. (28)

This paper analyzed the effect of preventive and therapeutic analgesic measures adopted during the trans-operative period and their impact on delirium. Pharmacological analgesic measures (dipyrone, morphine, hydromorphone, tramadol), co-analgesia anti-inflammatory agents (dexamethasone) and regional approaches (interventional) were not associated with a reduced incidence of delirium. However, a notable reduction in delirium was identified when children previously exposed to oral midazolam received diclofenac. Such statement should be carefully analyzed since it is the result of a selected group of patients (limited external validation), with prior midazolam exposure and using an observational methodology which is insufficient to be conclusive, but enough to debate and generate controversy in the area of the practitioner and academic anesthesiologist. We feel it is appropriate to associate multimodal analgesic strategies in accordance with the severity of the surgical procedure, and the probability to generate severe or chronic postoperative pain. Similarly, it is important to stress the



effect of regional analgesia techniques which showed a clinically significant reduction in the prevention of acute uncontrolled pain.

Expert groups have created and encouraged teams and clinical practice guidelines for the detection, prevention and timely treatment of pediatric emergence delirium. The guidelines published in the European Journal of Anaesthesiology in April 2017, by the European Society of Anesthesiology are a testimony to the hard work and huge interdisciplinary cooperation for the prevention of this outcome. (4) However, these guidelines fail to discuss controversial and relevant topics such as the nosological weaknesses, the lack of implementation of optimized scales for diagnosis, the need to enhance the knowledge about the population in each region, and the necessary active implementation of pharmacological and non-pharmacological strategies for the prevention of delirium; additionally, education and interventions are administered with a view to reducing parenteral separation anxiety. The fast evolution of neurological monitoring empowered with more accurate instruments and guided by multimodal anesthetic approaches, demands a mandatory and badly needed improvement of quality processes.

The results of this study have certain limitations that should be highlighted. The observational nature of the information hinders the analysis of the direct impact of oral midazolam as a premedication and its association with postoperative delirium. The lack of a control or comparative group represents additional statistical limitations.

## ETHICAL RESPONSIBILITIES

### Endorsement of the ethics committee

The study has been endorsed by the Committee of Ethics in Research with Human Beings of the Fundación Hospital Universitario de San José (CEISH-FHIUSJ), pursuant to minutes 077, dated April 20, 2017.

### Protection of persons and animals

The authors declare that no experiments in humans or animals were conducted for this research project. The authors state that the procedures followed were consistent with the ethical standards of the Committee for responsible human experimentation and with the World Medical Federation and the Declaration of Helsinki.

### Confidentiality of the data

The authors declare that they have followed the protocols of their work institutions regarding the disclosure of patient data.

### Right to privacy and informed consent

The authors declare that no patient data are included in this article. The authors declare that due to the ethical risk classification, the ethics committee of the research center of Fundación Hospital Universitario de San José (CEISH-FHIUSJ) did not require an informed consent. This document is in the possession of the corresponding author, of the investigators, and of the institutions involved.

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### Contribution by the authors

**VHGC, DSBA, WJGB, ILPV, JLCP, WSDD and IAM:** Study planning, data collection, interpretation of the results and drafting of the article.

**MATR:** Study planning, data collection, interpretation of the results.

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### Conflicts of interest

The authors have no conflicts of interest to disclose with regards to the project and the manuscript submitted.

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### Presentations

None declared.

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