



FACTORS ASSOCIATED WITH EMERGENCE DELIRIUM IN PEDIATRIC PATIENTS IN PERU: RESULTS OF A CROSS-SECTIONAL STUDY

FACTORES ASOCIADOS CON EL DELIRIO DE EMERGENCIA EN PACIENTES PEDIÁTRICOS EN PERÚ: RESULTADOS DE UN ESTUDIO TRANSVERSAL

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ABSTRACT

Introduction: Identify associated factors with emergence delirium in children in the Post-Anesthetic Recovery Unit of a Pediatric Health Specialized Institute in Peru. **Methods:** A cross-sectional study was carried out in children from 2 to 6 years old, physical status classification I and II, in elective procedures under anesthesia. The main variable was the presence of emergence delirium evaluated with the Pediatric Anesthesia Emergence Delirium scale greater than or equal to 10 points. To identify the factors associated with delirium, the Poisson regression model was applied and a p value < 0.05 was considered significant. **Results:** Of the 150 children, it was found that the incidence of emergence delirium occurred in 10.6%. Of these, 81.4% were under 5 years of age, pain was significantly associated in 37.5% with PR = 3.63, 95%CI [1.20, 10.1] and it was observed that 68,8% required palliative care. **Conclusion:** Pain was associated with delirium of postanesthetic emergence in children. Prevention and treatment of emergence delirium should focus on postoperative pain control and careful monitoring of patients after surgery.

Keywords: Emergence delirium; Anesthesia; Children; Palliative care. (Source: MESH-NLM)

RESUMEN

Introducción: Identificar los factores asociados al delirio de emergencia en niños en la Unidad de Recuperación Posanestésica de un Instituto Especializado en Salud Pediátrica del Per. **Métodos:** Se realizó un estudio transversal en niños de 2 a 6 años, clasificación del estado físico I y II, en procedimientos electivos bajo anestesia entre septiembre y diciembre 2022. La variable principal fue la presencia de delirio de emergencia evaluada con la escala Pediatric Anesthesia Emergence Delirium mayor o igual a 10 puntos. Para identificar los factores asociados con el delirio, se aplicó el modelo de regresión de Poisson y se consideró significativo un valor p < 0,05. **Resultados:** De los 150 niños, se encontró que la incidencia de delirio de emergencia se presentó en el 10,6%. De ellos, el 81,4% fueron menores de 5 años, el dolor se asoció significativamente en el 37,5% con RP = 3,63, IC95% [1,20, 10,1] y se observó que el 68,8% necesitó cuidados paliativos. **Conclusiones:** El dolor se asoció con el delirio de emergencia posanestésico en niños. La prevención y el tratamiento del delirio de emergencia deben centrarse en el control del dolor posoperatorio y en la vigilancia cuidadosa de los pacientes después de la cirugía.

Palabras clave: Delirio del despertar; Anestesia; Niños; Cuidados paliativos. (Fuente: DeCS- BIREME)

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INTRODUCTION

Emergence delirium (ED) is the alteration of the child's consciousness and attention to his environment with disorientation and perceptual alterations in the period immediately after anesthesia⁽¹⁾. The factors associated with ED in children are not precisely known, especially in developing countries like Peru. The incidence in postoperative children, according to world literature, ranges between 2% and 80%⁽²⁾. In Latin America and the Caribbean, the ED is reported between 13% and 56%⁽³⁻⁷⁾. In Cuba and Jamaica, it is between 13% and 56%; in Chile, Colombia and Ecuador it is between 13% and 39%.

It is estimated that the average occurrence of ED in postoperative children after the use of sevoflurane could be 30%, taking into account that some pathologies require multiple procedures in the operating room such as placement of venous access in difficult venous routes⁽⁸⁾. An agitated awakening can occur unexpectedly, causing the child to remove these accesses or hit the stretcher railings, generating discomfort when the father is present and stress in the staff in charge since they must focus their efforts on caring for more time the minor or requiring the use of more medications to control it, prolonging his recovery⁽⁸⁾.

There are several associated factors; nevertheless, in Peru, there are no published studies on the incidence of ED in the pediatric population. The results suggest that pain is the only factor associated with ED. Prevention and treatment should focus on postoperative pain control and careful monitoring of patients after surgery. Furthermore, this research was one of the first to include patients who required palliative care^(3,9-11). During the first half of 2021, the INSNSB (Instituto Nacional de Salud del Niño San Borja-by its name in Spanish) performed nearly 2,600 surgeries, which is a significant number in children, considering that local and global anesthesia societies are currently directing their efforts towards patient safety in anesthesia through the campaign for safe surgery.

The INSNSB is a national reference center at the third level of care in Peru. It is the only institution with a Pediatric Pain Therapy and Palliative Care Unit at the local level. The literature describes that children in

palliative care require multiple interventions under anesthesia¹². Worldwide, it is estimated that, according to differences in populations and types of studies, nearly 22 million children need palliative care^(13,14,15).

The objective of this study was to determine the factors associated with ED in children from the Post-Anesthetic Recovery Unit (PARU) of the Instituto Nacional de Salud del Niño San Borja (INSNSB). This can help identify patients at higher risk and take measures to prevent its appearance or treat it in a timely manner, thus limiting the undesirable consequences of their care, such as generating dissatisfaction among health personnel and parents.

METHODS

Study design

A cross-sectional and analytical study was carried out in the Post-Anesthetic Recovery Unit from the Instituto Nacional de Salud del Niño San Borja, from September to November 2022.

The study determined the temporal relationship between exposure to anesthesia and the presence of ED, evaluating the child's awakening in a single period in the immediate postoperative period. When these studies have a general analytical objective, the measure of association is the Prevalence Ratio (PR), especially when the prevalence of the effect is greater than or equal to 10%⁽¹⁶⁾.

Population

Patients aged 2 to 6 years 11 months 29 days, physical status classification ASA-PS (American Society of Anesthesiologists – Physical Status) I and II, undergoing procedures for head and neck surgery, chest surgery, pediatric surgery, were included. plastic and reconstructive surgery, gastroenterology, gynecology, hematology, pulmonology, neurosurgery, dentistry, ophthalmology, orthopedics and traumatology, otorhinolaryngology, interventional radiology, magnetic resonance imaging, tomography and urology.

Exclusion criteria: Children outside the age range, diagnosis of COVID-19, use of mechanical ventilation, medical history with incomplete data, physical status ASA-PS III onwards, previous diagnosis of behavioral



disorders, children with cognitive deficit, diagnosis of delirium before operating room, non-authorization of informed consent.

Variables

For the present study, age and sex were considered demographic factors, and as perioperative factors the ASA-PS classification, duration of anesthesia, diagnosis, procedure, premedication, type of anesthesia, analgesia, PAED score, Face, Leg, Activity, Cry, Consolability (FLACC) pain score and events as a result of the delirium. The presence of emergence delirium was evaluated with the PAED scale ≥ 10 points and pain with the FLACC scale ≥ 4 points. Both scales are widely validated, the first with a sensitivity of 64% and 86% specificity that can reach 100% when it is greater than 12 points^(1,17-20), and the second with a sensitivity of 94.9% and specificity of 72.5%^(21,22).

The PAED scale was studied with a committee of experts who described categories of ED behaviors. For content validity, various items were collected and statistically analyzed, resulting in 5 of them constituting this scale. For construct validity, the receiver operating characteristic curve was used⁽¹⁾.

The FLACC scale tested its validity by measuring changes in the scale in response to analgesics⁽²²⁾.

Procedures

Patients were selected from the surgical center's daily schedule, using simple random sampling until the sample size was complete. Demographic and perioperative data were collected from the medical records and from the observation of the child's awakening upon arrival at the PARU in digital data collection forms. The minors were observed during the first 20 minutes, from spontaneous eye-opening⁽¹⁾.

Programming in the operating room and images was daily, except on Sundays, holidays, and emergencies. The daily average of patients who arrived at the PARU between surgical and non-surgical programming performed under anesthesia was 30; for the purposes of this study, 50% of them were selected daily. For random sampling, the daily sampling frame was used, that is, random numbers were assigned to the list using the random function of the Excel program.

The list was ordered in ascending order according to the random numbers, then the researcher selected half of the first patients that corresponded⁽¹⁵⁾. The procedure was repeated until the required sample size was completed. If the selected patient did not meet the inclusion criteria, the next randomized patient was continued until the number of participants was completed.

Statistical analysis

Data were analyzed using Statistical Program for the Social Sciences version 25.0 (IBM SPSS Statistics, Chicago, IL). Univariate and bivariate descriptive statistics were used to analyze the data, including absolute and percentage frequencies, measures of central tendency, and dispersion. The data from the univariate analysis were presented in tables with numbers (n) and percentages (%); In addition, the median (measure of central tendency) and the IQR interquartile range (measure of dispersion) were calculated. For the multivariate analysis, a generalized linear regression model of the Poisson family with robust variance was applied to estimate the effect (prevalence ratio, PR) in both the crude and adjusted models, with their respective 95% confidence intervals, considering an alpha risk of 0.05. Two modeling scenarios were performed: the first model considered the main demographic and perioperative characteristics, while the second model considered the main factor of interest (pain), adjusted for covariates such as type of analgesia, type of anesthesia, and anesthetic agent. Data processing was performed using R statistical software and R Studio version 2023.06.2+561.

Ethical aspects

This research was carried out following the principles of Research Ethics and Scientific Integrity, which was registered and approved by the Universidad Nacional Mayor de San Marcos (Dictum No.: 000822-2022-UPG-VDIP-FM/UNMSM) and the Research Ethics Committee of the Instituto Nacional de Salud del Niño San Borja (Certificate No.: 036-2022, PI-654). The details of the study were explained to the guardian who accompanied the minor upon admission to the PARU, and verbal and written informed consent was obtained. The data collection sheets were numbered, coded and

uploaded to the REDCap platform to maintain their confidentiality.

RESULTS

150 children participated in the study. The majority (61.3%) were under 5 years of age and had an ASA-PS II classification (98%), there was a homogeneous distribution between both sexes (50.7% men and 49.3%

women), for 75 kids the procedure lasted a median time of 62 minutes (IQR = 35 - 140 minutes) and 14% (21) presented pain. The number of procedures was similar between those who underwent surgery and those who did not. Finally, during data collection, it was noted that about half (46.7%) had diagnoses requiring palliative care (see Table 1).

Table 1. Demographic characteristics and their association with emergency delirium in children in the Post anesthesia Recovery Unit of a Peruvian pediatric institution from September to December 2022.

Characteristics	Total		Emergency delirium			
	n=150	%	No = 134	%	Yes = 16	%
Years (age)						
2	37	24,7%	30	22,4%	7	43,8%
3	29	19,3%	28	20,9%	1	6,3%
4	26	17,3%	21	15,7%	5	31,3%
5	28	18,7%	27	20,1%	1	6,3%
6	30	20,0%	28	20,9%	2	12,5%
Classification ASA-PS						
I	3	2,0%	1	0,7%	2	12,5%
II	147	98,0%	133	99,3%	14	87,5%
Sex						
Masculine	76	50,7%	65	48,5%	11	68,8%
Feminine	74	49,3%	69	51,5%	5	31,3%
Duration of anesthesia (minutes)						
Median	62,0		64,50		56,0	
(IQR)	(35,0 - 140,0)		(65,0 - 128,75)		(37,50 - 147,50)	
Pain						
No	129	86,0%	119	88,8%	10	62,5%
Yes	21	14,0%	15	11,2%	6	37,5%
Procedure type						
Non-surgical	75	50,0%	68	50,7%	7	43,8%
Surgical	75	50,0%	66	49,3%	9	56,3%
Need for palliative care						
Yes	70	46,7%	65	48,5%	11	68,8%
No	80	53,3%	69	51,5%	5	31,3%

Source: Data obtained from the data collection form. ASA-PS: American Society of Anesthesiologists – Physical Status IQR: Interquartile Range

ED occurred in 10.6% (16) of the children. Of them, the majority (81.4%) were under 5 years old, male (68.8%), ASA-PS II (87.5%), and underwent a surgical procedure (56.3%). , needed palliative care (68.8%)

and 37.5% presented pain. The median duration of any procedure was 56 minutes (IQR = 37 - 147.5 minutes) (see Table 1).



Regarding the anesthetic characteristics, the majority registered midazolam as premedication (69.4%), the distribution of the type of anesthesia was similar between the use of inhalation and intravenous agent (48.7% and 46.8%, respectively), followed by the use of regional anesthesia (peripheral and caudal nerve block) in 4.5%. The most commonly used intraoperative analgesic strategy was metamizole (47%), followed by tramadol and morphine (31.2% and 14.6%, respectively). Regarding the anesthetic agent used, the main drugs used were sevoflurane, fentanyl and propofol (32.3%, 24.4% and 25.2%, respectively). On the other hand, 38.6% recorded permanence of health personnel and 36.4% recorded use of additional pharmacological therapy as a consequence of the ED

(see Table 2). When the bivariate analysis was performed according to the type of anesthesia, ED was observed mostly with inhalation and intravenous anesthesia (53.6% and 39.3%, respectively). A similar situation occurred when metamizole and tramadol were recorded as analgesia (60% and 25%, respectively), as well as in those who received sevoflurane, fentanyl, and propofol (35.7%, 26.2% and 21.4%, respectively). Regarding the consequences of the ED, 41.2% recorded permanence of health personnel, while there were no differences between those who registered additional pharmacological treatment and those who registered self-withdrawal from monitoring (29.4% and 26.5%, respectively). Only one child who lost venous access presented ED (see Table 2).

Table 2. Total multiple responses according to anesthetic characteristics and their association with emergency delirium in children in the Post Anesthesia Recovery Unit of a Peruvian pediatric institution, from September to December 2022.

Characteristics	Total		Emergency delirium			
	n	%	No	%	Yes	%
Premedication						
midazolam	25	69,4%	23	67,6%	2	100,0%
Ketamine	3	8,3%	3	8,8%	0	0,0%
Others	8	22,2%	8	23,5%	0	0,0%
Type of anesthesia						
Inhalation	130	48,7%	115	48,1%	15	53,6%
Intravenous	125	46,8%	114	47,7%	11	39,3%
Peripheral nerve block	11	4,1%	9	3,8%	2	7,1%
Caudal	1	0,4%	1	0,4%	0	0,0%
Analgesia						
Metamizole	116	47,0%	104	45,8%	12	60,0%
Tramadol	77	31,2%	72	31,7%	5	25,0%
Morphine	36	14,6%	33	14,5%	3	15,0%
Paracetamol	15	6,1%	15	6,6%	0	0,0%
Others	3	1,2%	3	1,3%	0	0,0%
Anesthetic agent						
Sevoflurane	132	32,3%	117	31,9%	15	35,7%
Fentanyl	100	24,4%	89	24,3%	11	26,2%
Propofol	103	25,2%	94	25,6%	9	21,4%
Remifentanil	25	6,1%	25	6,8%	0	0,0%
Ketamine	5	1,2%	5	1,4%	0	0,0%
Lidocaine	29	7,1%	23	6,3%	6	14,3%
Bupivacaine	9	2,2%	8	2,2%	1	2,4%
Others	6	1,5%	6	1,6%	0	0,0%
Consequences of suspected emergency delirium						
Requires permanence of health personnel	17	38,6%	3	30,0%	14	41,2%
Additional drug therapy	16	36,4%	6	60,0%	10	29,4%
Monitoring self-withdrawal	10	22,7%	1	10,0%	9	26,5%
Loss of venous access	1	2,3%	0	0,0%	1	2,9%

Source: Data obtained from the data collection form.



Likewise, it was found that the presence of pain is associated with ED, with an estimate of PR = 3.69 (95% CI: 1.25 - 9.92) in the crude model. The adjusted model's estimated effect was PR = 3.63 (95% CI: 1.20 - 10.1),

controlling for other covariates. All other covariates were not statistically significant ($p > 0.05$) in the crude and adjusted models (see Table 3).

Table 3. Estimation of the crude and adjusted effects of palliative, procedural and demographic care needs, and their association with emergency delirium in children in the Post anesthesia Recovery Unit of a Peruvian pediatric institution from September to December 2022.

Characteristics	Crude model			Adjusted mode		
	RP	CI 95 %	p	PR	CI 95 %	p
Pain						
No	-	-	-	-	-	-
Yes	3.69	1,25 - 9,92	0.01	3.63	1.20 - 10.1	0.02
Need for palliative care						
Yes	-	-	-	-	-	-
No	2.62	0,91 - 9,39	0.10	2.13	0,65 - 8,35	0.20
Age	0.77	0,53 - 1,09	0.20	0.82	0,56 - 1,18	0.30
Sex						
Masculine	-	-	-	-	-	-
Feminine	0.47	0,15 - 1,28	0.20	0.52	0,16 - 1,49	0.20
Duration of anesthesia	1.00	0,99 - 1,01	>0,9	1.00	0,99 - 1,00	0.40
Procedure type						
Non-surgical	-	-	-	-	-	-
Surgical	1.29	0,48 - 3,60	0,60	0.96	0,30 - 3,22	>0,9

Source: Data obtained from the data collection form.

Furthermore, the bivariate analysis shows that the estimate of the raw effect of pain on the presence of ED was PR = 3.69 (95% CI: 1.25 - 9.92), while in the adjusted model pain continues to be an associated factor (PR =

3.5, 95% CI: 1.15 - 9.77), controlling for other covariates of interest. However, no significant evidence of association ($p > 0.05$) was found in the study sample for the covariate type of analgesia (see Table 4).

Table 4. Estimation of the crude and adjusted effects of pain, type of analgesia and its association with emergency delirium in children in the Post anesthesia Recovery Unit of a Peruvian pediatric institution, from September to December 2022.

Characteristics	Crude model			Adjusted mode		
	RP	CI 95 %	p	PR	CI 95 %	p
Pain						
No	-	-	-	-	-	-
Yes	3,69	1,25 - 9,92	0.01	3,5	1,15 - 9,77	0.02
Analgesia						
Morphine	0,73	0,17 - 2,27	0,60	0,38	0,08 - 1,32	0,2
Metamizole	0,88	0,31 - 3,15	0,80	1,19	0,40 - 4,40	0,8
Tramadol	0,43	0,14 - 1,18	0,12	0,37	0,11 - 1,11	0,08

Source: Data obtained from the data collection form.



Finally, the diagnoses of the children requiring palliative care were grouped (70) and it was observed that four presented ED and seven had pain. Thus, the majority of disorders were hematological in 57% (leukemia, lymphoma, aplastic anemia). Of the four children who

presented with ED and required palliative care, half belonged to the group of hematological disorders; while, those who had pain were most from spinal disorders (scoliosis) followed by burns (see Table 5).

Table 5. Group of children with palliative care needs who experienced emergency delirium and pain in the Post Anesthesia Recovery Unit of a Peruvian pediatric institution from September to December 2022.

Diagnostic	Emergency delirium				Pain			
	No= 66	%	Yes= 4	%	No= 63	%	Yes= 7	%
Hematological disorder	38	57,6%	2	50,0%	39	61,9%	1	14,3%
Digestive tract disorder	13	19,7%	0	0,0%	13	20,6%	0	0,0%
Burn	5	7,6%	0	0,0%	3	4,8%	2	28,6%
Spine disorder	4	6,1%	1	25,0%	2	3,2%	3	42,9%
Solid organ tumor	2	3,0%	0	0,0%	1	1,6%	1	14,3%
Crouzon syndrome	1	1,5%	0	0,0%	1	1,6%	0	0,0%
Septicemia	1	1,5%	0	0,0%	1	1,6%	0	0,0%
Genetic syndrome	1	1,5%	0	0,0%	1	1,6%	0	0,0%
Airway disorder	1	1,5%	0	0,0%	1	1,6%	0	0,0%
Brain tumor	0	0,0%	1	25,0%	1	1,6%	0	0,0%

Source: Data obtained from the data collection form.

DISCUSSION

This study is one of the first local investigations to report results on factors associated with ED in a pediatric institution in Peru and included patients with diagnoses requiring palliative care.

It is highlighted that acute postoperative pain was statistically significant in association with the presence of ED in children admitted to the PARU. This result is similar to a study carried out in Brazil, where acute postoperative pain was found as a factor associated with ED in the multivariate analysis (PR = 3.91; 95% CI: 2.15 - 7.11; $p < 0.001$)⁽²⁾. In this regard, the aforementioned study conducted a survey in REDCap® where more than 70% responded that high levels of anxiety and untreated pain constituted risk factors⁽²³⁾.

The incidence of postanesthetic ED was 10.6%. This finding is within the wide range reported by the international literature of 2% to 80% and the most commonly proposed consensus range of 10% to 30%^(3,5-7,24,25). Also, it indicates a lower incidence of ED compared to other reports from Latin America and the Caribbean, where an incidence of 13% to 56% is reported. This difference between the various studies may be due to the different demographic characteristics and the multiple methodologies used.

Among children diagnosed with ED, more than half did not experience pain. This confirms that it can be present in non-painful procedures^(26,27), although several studies have reported that pain can occur in 45% of children with ED, after otorhinolaryngological

procedures^(18,28,29).

The reason for this association between pain and the pathophysiology of ED is still unknown; However, some authors suggest that changes in brain conduction between the thalamocortical and limbic systems make the brain vulnerable, depress higher-order attentional and executive networks, which implies dysfunctions in postoperative neurological brain activity⁽²⁾. It has been suggested that ether derivatives (sevoflurane, desflurane) have an almost 4-fold higher occurrence of ED compared to intravenous agents⁽³⁾.

It is believed that low blood/gas solubility inhalation agents produce excitation of the locus ceruleus⁽⁸⁾. Immaturity of the central nervous system and “early awakening” can also contribute⁽⁴⁾. The immaturity of the cholinergic (parasympathetic) centers of the hippocampus and the alteration of neurotransmitters (increase in dopamine or norepinephrine and decrease in acetylcholine) may provide an explanation for the susceptibility of younger children⁽³⁰⁾. Some authors postulate that this association found in the study could also be explained by the similarity of the items used in the PAED and FLACC scales⁽²⁸⁾.

Its main strength lies in the use of validated scales, PAED and FLACC, to measure the variables of interest (SD and pain, respectively). There is consensus that the use of the PAED scale improves research methodology in this area, particularly when postoperative pain is controlled⁽¹⁹⁾. Furthermore, it was observed that the use of both scales generated a favorable expectation among the PACU health personnel who were present during data collection, since it allowed early recognition of ED and pain. Although the INSNSB PARU “Postanesthesia Monitoring Sheet” currently uses the modified Aldrete scale for patient discharge, the institutional standard does not currently require the

application of these two scales. Therefore, it could be suggested that both scales be routinely used in post-anesthesia evaluation in different hospitals. This could facilitate further research and better planning of post-anesthesia awakening management and pain control.

It is important to note that although postoperative pain was the only factor associated with ED in this study, there are other factors that should be considered during medical evaluation. Future studies should continue to explore whether diagnoses requiring palliative care, age, type of procedure, and especially the use of specific anesthetic agents are associated with ED.

The study has the limitations that it was conducted at a single institution and had a cross-sectional design. Although these studies can be efficient in disease prevalence, short and inexpensive, they can lead to selection biases and make it difficult to verify the causal relationship. Besides, the sample size may be small to evaluate the association with other factors. In this sense, it is important to carry out multicenter studies.

It is possible that due to the sample size in the covariate subgroups and the imbalance in the distribution of the response variable, the association with these other factors was not evident.

Despite this, its main strength is that it sets an important precedent for future studies in pediatric anesthesia and pediatric palliative care in Peru, and comparative studies at an international level.

In conclusion, a significant association between ED and acute postoperative pain was observed in our study. Therefore, it is suggested that ED treatment should focus on postoperative pain control as well as careful follow-up of patients after surgery to detect this entity and treat it in a timely manner. Age, type of procedure, and anesthetic agent were not statistically significant.



Authorship contribution: LMUC has participated in all the study processes. JPMK, ARV, and CUQJ have participated in the approach to the methodology, analysis and interpretation of data, approving the final version of the manuscript, being responsible for the aspects to ensure its veracity and integrity.

Conflicts of interest: LMUC, ARV and CUQJ are members of the Instituto Nacional de Salud del Niño San Borja; however, they did not participate in any stage of the review process after the submission of this article.

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