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Original Research Article

Assessing the Effectiveness of Different Anesthetic Agents in Pediatric Patients: a Prospective Cohort Study

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Abstract:

Background: General anesthesia (GA) was required for surgical procedures involving millions of youngsters. Any possible dangers to neurodevelopment from pediatric anesthesia could pose a significant threat to public health. Numerous investigations on animals have demonstrated that GA, when often used, can cause a range of morphofunctional changes in the developing brains of young animals. To give a concise synopsis of preclinical research and compile the body of clinical research that has already been done, we carried out a systematic review. We considered research on kids who were under the age of eighteen and had their long-term neurodevelopmental effects assessed following one or more GA exposures. This study contains 72 clinical studies that were published between 2000 and 2022, with the majority of them (n = 58) being retrospective studies and coming from 18 different countries. After children are exposed to GA, two thirds of the studies (n = 48) show detrimental impacts on their neurocognition. Six domains are used to classify neurodevelopmental outcomes: achievement / academics, cognition, behavior/development, diagnosis, brain research, and others. The majority of research on children under 7 years old found negative neurocognitive consequences after GA exposure, although not all of the studies consistently corroborated the widely held belief that younger children were more vulnerable than older ones. Greater frequency and length of GA exposure, as well as significant surgical procedures, may suggest a larger chance of unfavorable results. Current research indicates that efforts must be made to restrict the amount, frequency, and duration of anesthesia as well as the dose of anesthetic medications. Future research calls for cohort studies with abundant data sources and suitable outcome measures, as well as meticulously planned and sufficiently powered clinical trials testing realistic therapies in pertinent patient groups.

Keywords: Anesthetic, Pediatric, Patients, Cohort.

Introduction

Even though there are standards for the administration of anesthesia, perioperative respiratory adverse events continue to be one of the most major causes of morbidity and death during paediatric anesthesia. [1,2] This is the case despite the fact that these guidelines have been produced. Parts I–IV There are a lot of reasons that contribute to their occurrence, some of which include the medical history of a child, the administration of anesthetic, and surgical operations. [3,4] There are specific risk factors for perioperative respiratory adverse events that have been described in previous studies; nevertheless, it is debatable whether or not children who are at a high risk are being detected in clinical practice. These risk factors have been characterized in previous studies. [5]

When there is an increase in airway sensitivity, which might be due to present asthma, a recent upper respiratory tract infection, or passive smoking, there is a high probability that the incidence of perioperative respiratory adverse events is associated with an increase in the number of adverse events that occur during the respiratory process. (2.5%–7%) As a result of the high prevalence of asthma in the paediatric population and the high incidence of upper respiratory tract infections in children who present for anaesthesia, anaesthetists are required to manage an increasing number of children who are at a high risk of experiencing perioperative respiratory adverse events in their day-to-day clinical practice. [6-9] This is because of the fact that the prevalence of asthma in the paediatric population is high. On the other hand, the bulk of paediatric research has focused on a specific population, a specific sickness (for instance, an infection of the upper respiratory tract), or the presence of specific sequelae, the most notable of

which is the laryngospasm that has been documented. [10]

During the preanaesthetic examination, if an accurate assessment of the risk of perioperative respiratory adverse events were performed, it would be able to modify the treatment of the anesthetic in order to reduce the likelihood of such complications arising. Because perioperative consultations are shifting from being based on medical principles to being based on nursing principles, it would be advantageous to have a pertinent risk assessment questionnaire that could be used in the preoperative setting. [11] This is especially true in view of the fact that nursing principles are becoming more prevalent in the United States. By giving a modified version of the International Study Group for Asthma and Allergies in Childhood (ISAAC) questionnaire to children prior to surgery, our goal was to determine whether or not there were any correlations between the history of the patient's family, the management of the anaesthesia, and the occurrence of perioperative respiratory adverse events. This was accomplished by administering the questionnaire to children. [12]

It is possible that the existence of agitation in particular children will make the process of emerging from general anesthesia (GA) more challenging. This, in turn, presents a challenging circumstance for the individual who is providing postanesthesia care. During this acute occurrence, the patient exhibits symptoms such as thrashing, crying or moaning, confusion, and incoherence (1–3). Additionally, the patient displays restlessness and agitation that is not directed toward a specific aim. It is common practice to use the terms "postanesthetic excitation," "emergence delirium," and "emergence agitation" (EA) interchangeably when referring to this acute episode. Additionally, it has been found that these unusual developing behaviors are frequently accompanied by the feeling of having paranoid thoughts (3). This is something that has been identified quite recently. [13] There is a possibility that the effects of EA will be severe and may result in the child experiencing bodily injury, particularly in the region where the procedure was carried out (2,4). Nevertheless, the problem will, in the majority of instances, go away on its own. Although there have been sporadic cases in which agitation and restlessness associated with EA have lasted for more than two days (5), the long-term psychological repercussions of EA are still unknown. This is despite the fact that there have been occasions in which EA has been experienced. [14]

Early epidemiologic studies revealed that the incidence of EA was 5.3% among all postoperative patients, with children having a greater frequency of the disorder (12%–13%) (6,7). This was the conclusion reached by the researchers. Despite the fact that this phenomena has been associated to particular anesthetics, in particular sevoflurane (8–14), a wide range of perioperative drugs (7,15–17), pain (10,18–21), and patient-related factors (22), the etiology of this occurrence is still unknown. The goal of this prospective cohort study was to determine the incidence of erectile dysfunction (EA), evaluate variables associated with and predictive of EA, and describe outcomes related to EA in healthy children who were undergoing general anesthesia (GA) for elective operations.

Research Methodology

Healthy children between the ages of three and seven who were undergoing general anesthesia for an outpatient surgical procedure were included in the study after receiving approval from the Institutional Review Board (IRB) and obtaining parental agreement. For the purpose of including all children with an ASA physical status of I–II who were cognitively intact, a nonprobability, consecutive-sampling strategy was utilized. Two distinct study periods, each lasting between four and five months, were used to enroll patients in order to minimize the likelihood of bias resulting from trends in clinical practice. A record of the child's demographic information as well as data concerning their medical and surgical history was taken prior to the operation. [15,16] All perioperative care was left up to the discretion of the anesthesiologist or other care providers in accordance with standard procedures, and it was not affected or altered on purpose as a result of the participants' participation in this study. From the perspective of the attending anesthesiologist, the child's behavior during the separation from their parents and the induction of general anesthesia was categorized as either peaceful and cooperative, mildly worried and emotional, or agitated and uncooperative. We noted the anesthetics and perioperative drugs, as well as the duration of the anesthesia and the time to awakening (that is, the time from the time the anesthetic was turned off to the time of initial alertness). While the patient was recovering from postanesthesia, a trained observer used a comprehensive checklist to document all of the behaviors that occurred throughout the procedure. [17] In addition, experienced nurses working in the postanesthesia care unit (PACU) reported the presence or absence of agitation with nonpurposeful movement, restlessness, or thrashing. This was characterized as agitation with or without thrashing; incoherence; inconsolability; and unresponsiveness. Children were not regarded to have EA if they complained of pain or experienced pain that was localized. [18] It was documented that the duration was recorded when EA was present. Additionally, detailed records were kept of all pharmacologic and nonpharmacologic interventions, adverse events, and the amount of time it took to discharge the

patient from the PACU. Criteria for discharge were established in accordance with standard operating procedure and were left up to the discretion of the PACU nurse. These criteria are comparable to Chung's (23) modified post anesthesia discharge scoring system. In addition, they incorporated the following: 1) the child's pain level can be easily managed at the discharge location; and 2) the child's fluid status is stable.
While their children were undergoing surgery, the parents of a subset of 250 children who had been recruited in a row completed the Behavioral Style Questionnaire for children aged three to seven years old (24). This standardized questionnaire provides a total of one hundred items, which, when added together, provide in numerical scores ranging from one (low/positive) to six (high/negative) for nine different aspects of temperament. It has been demonstrated that the questionnaire possesses sufficient reliability and validity across a wide range of populations. Numerous investigations, including clinical studies that were meant to evaluate the association between reaction to pain, hospitalization, and sedation (25–27), have made use of the instrument. Every caregiver was kept in the dark regarding their responses to this survey. Analysis of all of the data was performed using the SPSS® program (SPSS Inc., Chicago, Illinois). Data that are considered to be parametric, such as age, length of time under anesthesia, and temperament scores, are provided as mean standard deviations and were compared using unpaired Student's t-tests respectively. Comparisons of nonparametric data, such as sex and the use of anesthetics, were made using Chi-square tests in conjunction with Fisher's exact measurements. [19] There is a presentation of the relative risk (RR) and confidence intervals (CI) for any variable that has a significant association with EA. In order to determine the relative risk (RR), we compared the incidence of emphysema in the group that was exposed to sevoflurane to the incidence of emphysema in the group that was not exposed to sevoflurane. The anesthetic and demographic characteristics that were discovered to have a significant association with EA were incorporated into a logistic regression analysis in order to ascertain the independent risk factors for EA. A p-value of 0.05 was determined to be statistically significant. Several theoretical assumptions and basic recommendations for multiple regression (28,29) were utilized in order to ascertain the appropriate size of the sample for this particular research endeavor. In order to do an analysis of ten predictor factors, it is often appropriate to have a sample size of one hundred children who have the result (28,29). [20] Assuming that there is a 20% incidence of EA among children aged three to seven years old who are healthy, a sample size of five hundred would be required to obtain one hundred children who had this result. This sample size is sufficient to allow for meaningful analysis of ten predictor variables, and it is large enough to establish the incidence of this dichotomous variable (expected percentage, 0.20; precision, 0.10; confidence interval, 95% (30)). As a result of the fact that temperament was of secondary importance, and in order to lessen the burden that was involved with the completion of the Behavioral Style Questionnaire, this survey was only administered to fifty percent of the sample.

Results and Discussion

A total of five hundred twenty-one children took part in this research endeavor, which was carried out over the course of a single year. Eighteen percent of the people, or ninety-six percent, exhibit signs of EA. A breakdown of the sample's demographic information is provided in Table 1, which can be seen here. When compared to children who awoke without experiencing any agitation, those who manifested agitation were much younger and had a reduced probability of having previously undergone surgical procedures. The results of the temperament tests are presented in Table 2, which may be seen here. The ability to adjust was significantly lower in children who had experienced emotional arousal in comparison to children who had not experienced agitation. Among the children who underwent otorhinolaryngologic and ophthalmologic operations, respectively, EA was experienced by 42 children (26%) and 23 children (28%) who were treated for their condition. When compared to the number of children who suffered EA after undergoing urologic (15%), orthopedic (15%), general surgical (12%), and other (6%) procedures, this is a significant difference (P 0.02).

There was a correlation between a prolonged post anesthesia recovery and agitation that lasted for up to 45 minutes in certain cases (range, 3–45 minutes; mean, 14 11 minutes). Additionally, this agitation was connected with a longer duration of time for recovery (117 66 minutes versus 101 61 minutes for children who were not upset; P 0.02). A smaller percentage of these children were just restless and incoherent (14%), despite the fact that the majority of them were thrashing (86%) and kicking (64%). It was necessary for sixty percent of the children in the EA group to be physically restrained, which implies that they needed to be held down by a nurse. Furthermore, forty-two percent of the children required the assistance of two or more nurses before the level of agitation saw a reduction. There were 48% of cases in which the EA diminished without the need for pharmacologic intervention, and the duration of the EA in these children was shorter (11 minutes) than the duration of the EA in children who were treated (16 minutes; P 0.02). This was the case in children who were not treated. In comparison, just 77 (18%) of the children who were not agitated required intervention with an opiate or

benzodiazepine (P 0.0001), whereas fifty children (52%) required an opiate (n 46), benzodiazepine (n 2), or both (n 2). This implies that the children who were agitated required intervention with them. In conclusion, it is important to note that there were five adverse events that were associated with EA. There was an increase in bleeding from the surgical site (n 1), the removal of a surgical drain or an intravenous line (n 2), an increase in discomfort at the operating site (n 1), and a minor injury to the nurse (n 1). These were some of the complications that occurred during the procedure.

Table 1. Demographics and Characteristics of the Study Groups

Variable	EA (″96)	No EA (″425)	*P* value
Age (yr)	4.8 2	5.9 3.3	0.002
Male sex	51 (53%)	258 (61%)	0.172
ASA I (%)/ASA II (%)	69 (72%)/27 (28%)	264 (62%)/161 (38%)	0.072
Had previous surgery	45 (47%)	254 (60%)	0.015
Difficulty separating[a]	4 (7%)	51 (6%)	0.86
Uncooperative at induction[a]	12 (13%)	48 (12%)	0.79

Table 2. Mean Temperament Scores of the Study Groups

Variable	EA (″55)	No EA (″186)
Activity	3.7 0.5	3.6 0.7
Rhythmicity	3.2 0.6	3.2 0.6
Approachability	3.1 0.7	3.0 0.8
Adaptability	2.6 0.5*	2.8 0.8
Intensity	4.3 0.5	4.3 0.6
Mood	3.2 0.7	3.2 0.7
Persistence	3.1 0.7	3.0 0.6
Distractibility	3.8 0.8	3.8 0.7
Threshold (sensitivity)	3.7 0.6	3.7 0.6

The link between perioperative variables and the presence of EA is outlined in Table 3, which can be seen here. Children who were treated with sevoflurane or isoflurane, as well as those who underwent procedures in ophthalmology or otorhinolaryngology, were considerably more likely to suffer euphoric episodes than children who did not undergo these procedures. The use of sodium pentothal, on the other hand, was linked to an occurrence of EA that occurred less frequently. When compared with children who had another anesthetic regimen, those who received a combination of sevoflurane and isoflurane for induction or maintenance had, on average, a greater than twofold increased likelihood of experiencing epigastric anesthesia (P 0.0001). When compared to children who were not disturbed, there was a significant difference in the percentage of children who had received intraoperative analgesics (98%) who had experienced EA. Between children who had undergone EA and those who did not, there was no difference in the length of time that they were under anesthesia (61 minutes and 28 seconds versus 68 minutes and 48 seconds, respectively). The time it took for children with EA to wake up was considerably less than that of children without EA (14 minutes versus 26 minutes and 23 seconds; P 0.0001). [21,22]

An increased incidence of EA was found to be related with ten different variables, according to the findings of a univariate analysis. Young age, lack of previous surgical experience, inability to adapt, ophthalmology operations, otorhinolaryngology procedures, sevoflurane, isoflurane, sevoflurane/ isoflurane, analgesics, and a short time prior to awakening were among the factors that contributed to the patient's condition. This information, along with the interactions between the components, was subsequently incorporated into a logistic regression model that utilized backward selection. With the help of multivariate analysis, we were able to identify three of these characteristics that were predictive of EA. There is a description of these in Table 4. [23]

Table 3: Incidence of Emergence Agitation (EA) Relative to Perioperative Factors

Variable	EA (*n*96)	*P* value[a]	Relative risk (95% CI)[b]
Surgical procedure Ophthalmologic (*n*83)	23 (28%)	0.017	1.66 (1.1–2.5)
Otologic (*n*164)	42 (26%)	0.004	1.69 (1.2–2.4)
Anesthetic(s) received Sevoflurane (*n*236)	57 (24%)	0.002	1.77 (1.2–2.6)
Isoflurane (*n*300)	68 (23%)	0.004	1.78 (1.2–2.7)
Halothane (*n*282)	44 (16%)	0.07	NA
Propofol (*n*62)	6 (10%)	0.06	NA
Sodium pentothal (*n*35)	2 (5%)	0.03	0.26 (0.07–1.0)
Induction/maintenance drugs Sevoflurane/isoflurane (*n*145)	44 (30%)	0.0001	2.2 (1.5–3.1)
Sevoflurane/sevoflurane (*n*20)	4 (20%)	0.77	NA
Sevoflurane/halothane (*n*48)	6 (13%)	0.26	NA
Halothane/isoflurane (*n*83)	19 (23%)	0.26	NA
Preoperative midazolam (*n*80)	12 (15%)	0.419	NA
Intraoperative analgesics (*n*460)	94 (21%)	0.001	6.2 (1.2–25.6)
Anticholinergics (*n*30)	8 (8%)	0.23	NA

Table 4: Factors Predictive of Emergence Agitation

Variable	Wald statistic	*P* value
Time to awakening	24.851	0.001
Isoflurane	6.339	0.012
Otorhinolaryngologic procedure	5.191	0.023
Ophthalmologic procedure	3.643	0.056
Adaptability	2.995	0.084

In general, the volatile anesthetics (sevoflurane and desflurane) have been the principal focus of the majority of the research that has been conducted on the topic of EA as a postoperative complication in children (8–11,14,21,31–36). The incidence of EA in children who received these anesthetics has been reported to range anywhere from 24 percent to 66 percent; however, it is impossible to compare the results of these investigations due to variances in methods, as well as differences in the diagnosis and classification of EA during these research. In point of fact, a recent study conducted by Cole et al. (37) demonstrated that the incidence of EA increased from 10% to 30% in a single sample when the criteria of EA was broadened to include infants who were sobbing and inconsolable, as well as children who were restless and disoriented. In spite of this, the majority of the data suggests that anesthetics that have a poor solubility are linked to an increased incidence of agitation that is, in some way, connected to abrupt awakening. [24] In the same way that these studies found that a short time to awakening and the use of sevoflurane were associated with a common occurrence of EA (24%) in patients, our findings are consistent with those studies. Additionally, we revealed that the maintenance with isoflurane was strongly associated with better outcomes.23 percent of the time, agitation is used. The findings of the research conducted by Cravero and colleagues (13) demonstrated that although sevoflurane led to a more rapid emergence, the time it took for the patient to be discharged was significantly greater than that of halothane. It appears from this that the benefit of speedy emergence can be rendered null and void if there is a significant amount of agitation present throughout the emerging process. [25] The emergence times of the sevoflurane and halothane groups are shorter, but there is no difference in the discharge times between the two groups (9,31,34). [26,27] This finding is consistent with the findings of other researchers who have made similar discoveries. During the course of this research, we came to the realization that it was EA that significantly extended the amount of time that the patient was kept in the PACU. It is possible that this was the outcome of additional pharmacologic treatment in addition to other supportive therapies that were necessary in order to bring the patient's agitation under control.

A number of studies have hypothesized that the extreme pain that is experienced during times of altered consciousness might be a contributing factor in the development of severe EA in certain children (35,36).[28] However, a conclusive connection between the two has not been demonstrated (3–5,12). The use of ketorolac, acetaminophen, tramadol, or fentanyl has been shown to reduce the agitation that is associated with sevoflurane anesthesia in children who are undergoing otorhinolaryngology surgery (10,18–21). This has been established through a number of studies. According to this discovery, there may be a correlation between experiencing pain and experiencing euphoria. However, Murray et al. (34) shown that preemptive oxycodone reduced

postanesthesia agitation in children who had received halothane. However, it did not have the same effect on children who had gotten sevoflurane as it did on children who had received halothane. Furthermore, a number of investigations have revealed that there is a clinically significant incidence of EA in patients who are nominally pain-free [3,5,9,12,14,22] which shows that analgesics are unable to totally eliminate postanesthetic agitation. [29] A number of studies have sought to differentiate pain-related agitation from other kinds of agitation by incorporating pain scales, in addition to agitation measures, into the methodology [9,20,35]. This is despite the fact that it is still difficult to differentiate between the two types of agitation. Children were judged to have emotional and behavioral issues (EA) if they demonstrated actions that were characteristic of agitation but did not express or complain of experiencing discomfort. This was the conclusion reached by the researchers of this study. [30] Furthermore, a prophylactic analgesic was given to 98% of the children who had experienced EA, and in 48% of the cases, the agitated behaviors were eased without the need for any types of pharmacologic intervention. This was the case in all of the cases. In spite of the fact that it is not feasible to totally eliminate the likelihood that pain is a factor that contributes to EA, these data suggest that there is a potential that another mechanism is at play. Pain can be a potentiating factor for agitation, especially in the case of children who are undergoing brief surgical operations, for which the peak effects of analgesics may not be experienced until a considerable amount of time after they have awakened. It is essential to take into consideration the fact that pain can be a potentiating factor for agitation.

Conclusion

We have found that more studies reveal numerous anesthetic exposures in early childhood, which are accompanied by an elevated risk of neurodevelopmental damage. This was discovered by a review of the literature that is currently available. On the other hand, the majority of these indicators merely indicate a moderate risk of adverse consequences, with a hazard ratio that does not exceed 2. Furthermore, it is worth noting that three extensive investigations, namely GAS, MASK, and PANDA, offer substantial evidence that a single exposure lasting less than one hour does not have any correlation with long-term neurodevelopmental problems. Furthermore, despite the fact that the current findings are comforting, it is impossible to ignore the possibility of neurotoxicity associated with anesthetic operations without reaching a definitive conclusion (Hansen, 2015). As a result of this worry, it is essential for clinical practice to make every effort to restrict the duration of anesthesia, the number of times it is administered, and the amount of anesthetic drugs that are administered. Additionally, it is possible to take into consideration alternate and mitigating remedies. In order to conduct future research, we need cohort studies that have a wealth of data sources and acceptable outcome measures, as well as clinical trials that are meticulously organized and sufficiently powered, and that test feasible therapies in patient populations that are relevant to the research.

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