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Effect of General Anaesthesia on the Developing Brain: a Pilot Study

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INTRODUCTION

Anaesthesiology is still a young yet growing specialty, especially regarding its long-term effects on the pediatric population and their developing brain. The delayed effects are still under study because potential interventions cannot be studied directly on humans especially on the pediatric population. Anesthesia in newborn infants is sometimes necessary as newborn infants may require surgeries that can not be postponed. Although the development of the brain begins during the last semester of intrauterine life, the brain is not fully developed at birth and continues to grow up to the age of 2 years. It has been studied and widely accepted that the commonly used general anesthetics potentiate inhibitory transmission through gamma-amino-butyric-acid type A ($GABA_A$) receptors and the excitatory transmission is reduced through *N*-methyl-D-aspartic acid (NMDA) glutamate receptors causing widespread apoptotic neurodegeneration.[1] The adverse effect of halothane on the developing brain was reported some two decades ago when it was studied and accepted that long-term exposure to an inhalational agent like halothane, beginning in utero and continuing for several days in the postnatal period, caused impairment of synaptogenesis, reduction in dendritic branching, suppressed axonal growth and reduced myelinated nerves in rodents.[2] Studies in some young animals and human primates have shown that several drugs used for general anesthesia, at therapeutic concentrations used for anesthesia,

killed cells, and produce neurodegeneration much before anesthesia when the brain is undergoing developmental changes.[1] Studies done on the adults have shown that $GABA_A$ receptor activation leads to an influx of chloride ions (Cl^-) into the cell, this results in hyperpolarization and can lead to neuroprotection in many models during the period of hypoxia, ischemia, and other forms of cerebral insults. However, during the early stage of life when the brain is still developing, especially during synaptogenesis, the intracellular concentration of Cl^- is high; activation of $GABA_A$ receptor may result in Cl^- efflux, and depolarization of neurons.[2]
As per the above studies, there are chances that general anesthesia including halothane can affect the developing brain of young children. In this retrospective observational study, we intended to study the effect of general anesthesia using halothane predominantly on the developing brain of young children undergoing surgery for cleft lip, cleft palate, or both.

DISCUSSION

The pediatric population belongs to a very uncertain group of patients since the physiologic processes that affect drug utilization and metabolism undergo rapid changes as children grow and mature. Therefore, the use of various pharmacologic drugs in pediatric patients requires special considerations.[3] The issue of anesthesia-related neurotoxicity has been a topic of the current discussion, and parents are very concerned about the effects of general anesthesia on their child's growth and brain development. There is much convincing preclinical evidence in rodents and nonhuman primates that anesthesia agents in common clinical use are neurotoxic to the developing brain *in vitro* and can cause long-term neurobehavioral abnormalities *in vivo*. Other than the animal data, various human cohort studies illustrate the associated outcomes of long developmental before associated outcomes long before outcomes another long-term the pediatric population who underwent major surgery during their neonatal period. [1]
This review summarizes what conclusions can be drawn from the existing studies in the literature and how these studies stand up with our findings.
The topic has been contentious since the advent of anesthesia; with contradictory evidence arising with continuing research. In our brief study, which is to be followed with multicentric larger data collection, we found that there was a significant difference between all the parameters evaluated which were physical activities, motor (gross or fine), academics, behavior, and other areas of interest. We used a scale of 10 for complete developmental parameters as it would encompass almost the entire spectrum of brain development and also because we could reciprocate the same in our local native language which parents could understand easily. Finding significance in all the parameters was a little unexpected, hence we repeated the questionnaire randomly among 25 patients with a neutral blinded observer. Also, our study found that there were lesser scores in those exposed within 1 year and in those who were exposed multiple times, though these were not statistically significant.
Young children when exposed to a brief, single anesthetic did not show any evidence of adverse long-term effects on the developing brain, according to a Danish study conducted in 2011. The relevance of using animal data for humans undergoing surgery under anesthesia early in life remains uncertain, partly due to the difficulty in studying and differentiating anesthetic exposure

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and its pathological impact in the animals to clinically useful effects in patients, but the data cannot be fully ignored.[4] In 2000, Ikonomidou et al published a study investigating the mechanism behind et almuch-before anesthesia long-term Alcohol Syndrome (FAS) development. By treating rat pups with ethanol during the peak period of brain synaptogenesis, they were able to replicate the effects of FAS like generalized loss of brain mass and neuronal apoptosis. They found that ethanol causes widespread apoptotic neurodegeneration by two different mechanisms: N-methyl-D-aspartate (NMDA) antagonism, and γ-aminobutyric acid receptor ($GABA_A$) activation. This study caught the attention of the number of anesthetists, as many of the anesthetic agents and sedatives act by one or both of these mechanisms.[2]

Over the previous years, several studies done in various animal models including rodents and non-human primates have strongly shown a link between anesthetic agents and neuroapoptosis. Mostly all of our commonly used anesthetic agents have been identified as culprits, including inducing agents, volatile anesthetics, and nitrous oxide.[5] The General Anaesthesia compared to Spinal Anaesthesia (GAS) trial is an international, multicentre, observer-blinded, randomized controlled trial in which pediatric population (less than 60 weeks postmenstrual age, born greater than 25 weeks gestation) undergoing inguinal hernia repair were randomly assigned either to sevoflurane general anesthesia or awake-regional anesthesia by spinal, caudal, or combined spinal-caudal technique. The primary outcome was the score on a validated Intelligence Quotient (IQ) test dispensed at age of 5 years. The secondary effects were recently reported in *Lancet*, assessing neurodevelopment at age 2 years by grading cognitive skills such as attention, memory, and problem solving, in addition to motor and language skills. They found no evidence that less than one hour of sevoflurane anesthesia in infancy increases the risk of adverse neurodevelopmental outcomes long-term at age 2 compared to the awake-regional group.[6]

Sun et al published another milestone trial, the Paediatric Anaesthesia Neurodevelopment Assessment (PANDA) study. This study compared neurocognitive and behavioral outcomes in children aged 8–15 years old exposed to a single general anesthetic for inguinal hernia surgery before age 3 to their unexposed sibling. The result suggested no statistically significant difference in full-scale IQ scores between the exposed and unexposed siblings. There were also no statistically significant differences between groups because of memory, executive function, motor, and processing speed, language, attention, visuospatial function, or behavior. The results reported were powered by the study's use of sibling-matched controls (which reduced confounders, e.g., genetic makeup, socioeconomic status, and parental education) and the ability to recheck the anesthetic record, which provided detailed insight into the type and duration of anesthetic exposure.[7] O'Leary et al published a large population-based cohort study showing developmental outcomes at primary school age (age 5–6) in over 28,000 children exposed to general anesthesia compared to more than 55,000 matched controls. In the first "big data" study, they found no evidence of adverse developmental outcomes in children exposed to anesthesia before the age of 2 years, or in those given multiple exposures to anesthesia. While there was a very small risk of adverse developmental outcomes in children exposed after age 2, the significance of this finding remains unclear.[8,9]

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In 2011, Hansen and colleagues assessed ninth-grade standardized test scores in over 2,500 children who underwent inguinal hernia repair in infancy and compared to age-matched controls, there was no evidence of increased learning disabilities when adjusting for known confounders. The author later showed that over 700 infants given anesthesia for pyloric stenosis repair before 3 months of age had similar educational test scores in adolescence compared to the unexposed controls of the same age.[10]

Bartels and colleagues conducted a monozygotic concordant-discordant twin study of over 1,000 twin pairs in which one sibling was exposed to anesthesia before outcomes long before outcomes and outcomes another sibling was unexposed. They found the exposed twin had similar scores on standardized tests at the age of 12 years as the genetically identical unexposed twin, suggesting that anesthesia exposure was not a risk factor for low test scores.[11]

These studies thus refute any long-term much deleterious effect of Anaesthesia on the developing brain, a finding which has numerous confounding factors including environmental, socio-economic, and genetic makeup. To nullify environmental and socio-economic factors, we used classmates of cases as controls in this study. On the contrary, there is also strong evidence of anesthesia-related neurodevelopmental diminution.

Wilder et al conducted a study and examined several surgical procedures in infants under three years of age, while Kalkman et al specifically focused on infants who had urological procedures before the age of two years. The endpoints taken in the two studies were contrasting. Wilder et al used reports of learning disability of any kind as the endpoint. The study findings were based on linking the data on learning disability in the Olmsted County birth cohort with the numerous medical and anesthesia records to which the investigators were able to correlate. This has allowed for the detailed analysis of the specifics of anesthetic exposure, including the type of agents, the duration, and the frequency of exposure. Kalkman et al used a questionnaire on child behavior to unusual behaviors as the endpoint for their study. These studies provide implicative evidence that anesthetic exposure at a young age may be associated with increased risk for learning disability later when there has been more than one exposure; and aberrant behavior. [9]

In the study of Departments of Anaesthesiology and Epidemiology, Columbia University College of Physicians and Surgeons and Mailman School of Public Health, New York, Children with general anesthesia exposure of 35 min had no difference from unexposed children, but those with exposures >35 min had lower total and expressive language scores. It remains uncertain if this is a dose-response relationship, or if children requiring a longer duration of exposures for surgeries have other clinical reasons for lower scores.[12]

Backeljauw et al in their study compared healthy participants of a language development study at age 5 to 18 years who had undergone surgery with anesthesia before 4 years of age (n = 53) and compared them with unexposed kids (n = 53) who were matched for factors like age, gender, handedness, and socioeconomic status. Neurocognitive assessments included the Oral and

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Written Language Scales and the Wechsler Intelligence Scales, as appropriate for age. Brain structural comparisons were done by using T1-weighted MRI scans. Their outcome suggests that general anesthesia for a surgical procedure at a young age may be associated with long-term accentuation of language and cognitive skills. In a study by Flick and co-workers, they found that exposure to anesthesia/surgery before the age of 2 was a risk factor for the development of Learning disabilities, thus corroborating with our study. They also found the need for an individualized education program(IEP) for speech/language impairment in children with multiple, but not single, exposures, a finding which is similar to ours, though we had really small data. A similar pattern of results was observed for most scales of group-administered tests of cognitive skills, but not the need for an IEP for emotional/behavioral disorders.[14]

Ing et al studied long-term differences in language and cognitive function after childhood exposure to anesthesia. They analyzed the Western Australian Pregnancy Cohort (Raine) Study, which included 2868 children born from 1989 to 1992. Of 2608 children examined, 321 were exposed to anesthesia before age of 3years, and 2287 were unexposed. Their results suggested that the association between anesthesia and neuropsychological outcomes may be present, though confined to specific domains. Children in this cohort exposed to anesthesia before the age of 3 years had a higher relative risk of language and abstract reasoning issues at the age of 10 years than unexposed children.[15]

Thus we observe there is confounding evidence with relation to this topic. As researchers all over keep on discussing and debating the topic we should consider advisories from various statutory bodies. Taking FDA as a significant international guiding authority on drugs and its human influence we should look into what it advises concerning pediatric anesthesia and that becomes significant justification to our findings that there is the possibility of ill effects of anesthesia on developing brains.[16]

In the safety announcement of 2017, they have added the warning to multiple anesthetic agents regarding the possibility of negative influence on brain development in children younger than 3 years and have instructed to add labels highlighting the same long-term outcomes another much-before anesthesia long-term special regarding. They have also suggested delaying elective surgeries to beyond 3 years of age whenever medically possible. Among other volatile anesthetic agents (sevoflurane including) this list includes halothane, which we used in our cases, and also propofol which is probably the most commonly used induction agent in all age groups. Anesthesia involves multiple drugs and pinpointing a particular drug for a specific side effect becomes impossible. To encourage further research on the same subject FDA has started the SmartTots initiative where different agencies from the world over will research simultaneously on this to have large data for significant inference.

Childhood general anesthesia typically comprises single short exposures and is likely to carry low risk However, if general anesthesia is thought to have long-term neurodevelopmental risks, then the impacts on clinical practice could be far-reaching. In considering the current clinical implications, it should be noted that the evidence base consists mainly of retrospective observational studies and is wrought with numerous confounding factors.

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Since our study was carried out on a small group and taking into consideration the various studies in this field with both positive and negative results, the conclusion can not be made. Although in our study we found that there was some developmental deficit among the children undergoing surgeries at an early stage of life under general anesthesia. Although our study and other observational studies have some limitations. At this point, we cannot exclude the possibility that exposure to anesthesia/surgery may adversely affect neurodevelopment. Based on this we cannot ignore the ill consequences of general anesthesia on pediatric patients. But further studies are needed on a larger scale to study the effect of general anesthesia and its safety on the developing brain.

MATERIALS AND METHODS

TABLE 1: PARAMETERS STUDIED

PARAMETERS Each Parameter having a maximum of 10 score	**DESCRIPTION**	**QUESTIONNAIRE** Good: 2 Points, OK: 1 Point, Bad: 0 Point For each Question
Physical activities	*Sportsmanship, cooperation, gross motor skills*	1. *The child plays calmly and quietly* 2. The child participates in planning and preparing for task/ games 3. walks perfectly or stumbles 4. works gracefully or clumsy 5. ease in learning new skills like catching, skating, etc
fine motor skills	*fine motor skills*	1. *likes to draw/ ease in drawing/ represents well through drawing* 2. ease in pouring water into the glass 3. avoiding spillage of food while eating 4. ease in holding pen/ pencil 5. ease and quickness in buttoning/tying shoelaces
Other fields of interest	*Music/ dance/mind games, indoor games, etc*	1. *concentration* 2. participation 3. ease in starting on tasks 4. ease in socializing 5. ease in learning and

		remembering
Academics (score)	*Reading and writing*	*1 .acquiring reading skills* 2. ease in understanding 3. interested and independent in doing homework 4. less spelling mistakes 5. ease with mental arithmetics
Social and emotional behavior	*Understanding and conversation(irritable/ respectful/ anger/happiness)*	*1. well behaved in the social gathering* 2. easily makes friends 3. makes eye contact 4. easy going with changes in daily routines 5. kind and respectful language

Data collected was transformed into an MS excel sheet for further processing and analysis. Appropriate statistical software and tools were used and data analyzed. Parametric and nonparametric tests of significance were used accordingly to find the association between different qualitative and quantitative variables of interest P-value less than 0.05 was taken as statistically significant.

TABLE 2: DIFFERENCE BETWEEN GROUPS CONCERNING PARAMETERS EVALUATED

Group Statistics

group		N	Mean	Std. Deviation	pvalue
Physical Activity	1	100	7.13	1.203	.000
	2	100	8.18	.809	
Motor Skills	1	100	9.97	.171	.048
	2	100	10.00	0.000	
Behavior	1	100	6.70	1.605	.000
	2	100	7.93	.640	
Academics	1	100	6.15	1.660	.000
	2	100	7.99	.882	
Other	1	100	3.88	1.966	.000
	2	100	5.73	1.205	

As shown in the above table, in all aspects of comparison between the two groups p-value was statistically significant. Thus, the result of our studies shows that there are some developmental deficits among the children undergoing surgeries under general anesthesia including halothane as the inhalational agent as compared to the children who had not undergone any surgeries.

TABLE 3: NUMBER OF CHILDREN WITH FIRST ANESTHESIA EXPOSURE LESS THAN 1 YEAR AND MORE THAN 1 YEAR

LESS THAN ONE YEAR	MORE THAN 1 YEAR
70	30

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TABLE 4: DIFFERENCE IN PARAMETERS BETWEEN CONCERNING AGE OF EXPOSURE

group	age(years)	mean	SD	P-value
physical	<1	7	1.41	>0.05
	>1	6.6	0.69	
motor	<1	9.95	0.22	>0.05
	>1	10	0	
behavior	<1	6.85	1.72	>0.05
	>1	6.7	1.33	
academics	<1	5.3	1.6	>0.05
	>1	6.7	1.56	
others	<1	3.65	2.02	>0.05
	>1	4.8	2.21	

TABLE 5: DIFFERENCE IN NUMBER OF CHILDREN UNDERGONE SINGLE VS MULTIPLE ANAESTHESIA EXPOSURE

SINGLE	MULTIPLE
40	60

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TABLE 6: DIFFERENCE IN PARAMETERS BETWEEN CONCERNING NUMBER OF ANAESTHESIA EXPOSURES

group	exposure	mean	SD	P-value
physical	single	7.4	0.68	>0.05
	Multiple	6.6	1.43	
motor	single	10	0	>0.05
	Multiple	9.95	0.22	
behavior	single	6.6	1.74	>0.05
	Multiple	6.5	1.36	
academics	single	6.5	1.58	>0.05
	Multiple	5.8	1.62	
others	single	3.8	2.25	>0.05
	Multiple	3.95	2.04	