THE EFFECT OF GENERAL ANESTHESIA ON NEUROCOGNITIVE DEVELOPMENT IN EARLY CHILDHOOD

April 3, 2012

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Background: There are three subdivisions of anesthetics including hypnotics, sedatives, and analgesics. Earlier studies on animals showed a negative relationship between anesthetic administration and learning as well as neurodegeneration. The human brain is most susceptible to damage when peak synaptogenesis occurs, which is prior to the age of three.

Objective: To determine the effect of general anesthetics on neurocognitive development in children under the age of twelve. To examine if the current practices of general anesthesia administration need revision. Finally, the applicability of general anesthetic administration to children under six in the dental field will be explored.

Methods: An electronic literature search was completed using the Ovid Medline database to obtain applicable research papers. A lecture series by an expert in the field was attended at Hospital for Sick Children, Toronto. The entire research process was supervised by a tutor according to guidelines found in the Evidence-Based Care Module Student's Manual (2011-2012) of the Clinical Epidemiology Community Dentistry Course at the Faculty of Dentistry, University of Toronto. A systematic review was completed on the relevant research articles that were found.

Results: The studies looked at children aged four and under in two cities in the United States who were undergoing a variety of surgical and diagnostic procedures involving general anesthetics, mainly halothane and nitrous oxide. Quantification of learning and neurodevelopment was based on academic aptitude tests and negative behavioural outcomes. Children exposed to general anesthesia before the age of four had an increased risk of developing learning disabilities and this effect was dose dependent.

Conclusions: There was a mild to moderate association but no causal relationship between early exposure to general anesthetics in children and the development of learning disabilities.

Keywords: general anesthesia, children, neurodevelopment, learning

1. Background

1.1

General anesthesia is utilized for both elective and non-elective surgeries on children. Due to the nature of a child's developing brain, it is imperative that the effects of anesthesia be quantified and qualified to ensure that the general anesthesia provided is more heavily weighted towards beneficial on a risk benefit analysis. Based on the findings, best practice recommendations can be formulated.

1.2

Seminal study:

Literature has demonstrated that exposing animal models to different forms of general anesthetics adversely affect neurodevelopment in addition to cognition. For example, *Ikonomidou et al.* demonstrated that blocking NMDA receptors in the developing rat brain caused apoptosis and neurodegeneration [1]. In other animal models, similar observations confirmed neurodegeneration with exposures of ketamine to the developing monkey brain[2]. With respects to cognitive impairment, water maze studies that evaluate learning behaviour, indicate that early exposures of anesthetics to the developing rat brain led to persistent learning deficits and difficulties in completing water maze tasks [3]. Although research has clearly indicated impairment to neurodevelopment in animal studies, it has yet to clearly establish the link between the effects of general anesthetics on the developing brain in a human model.

Neurodevelopment and synaptogenesis:

The developing brain undergoes the processes of neurogenesis, migration, synaptogenesis, apoptosis and myelination as it fully develops. Each process of neurocognitive maturation follows a strict timeline. Synaptogenesis is a process by which synapses are formed throughout the brain. Synapses connect the axons with their target cell surfaces and they have been shown to be the primary condition for learning rather than the result of learning. Synapses form the foundation for neural transmission and are thought to preserve the neuron's integrity. Once synapses are broken and neural transmission is impeded, degeneration occurs which can manifest in a variety of ways ranging in severity [4].

The development of a human child's brain begins at the primary sensorimotor cortex and concludes with the development of the prefrontal cortex. At birth, the child's peak synaptogenesis in the primary sensorimotor cortex develops. At the nine month period, the parietal and temporal association cortex areas are established. These areas are specifically pertinent to the language and spatial development of the child. Once the child reaches the age of three, the prefrontal cortex controlling executive, integrative and modulatory brain function is developed. Since synaptogenesis is critical to the proper cognitive development of the child, it is necessary to investigate treatment techniques or applications that may influence or hinder normal development. An insult occurring early in the developmental process could potentially affect the specific brain region undergoing the synaptogenesis as well as delay the development of future brain functions. As will be shown in the following paper, exposure of anesthesia to the developing brains of children may cause neurodegenerative changes that adversely affect learning and behaviour. This in turn may require amendments to be made in the current practice when administering general anesthesia to children. [5,6,7,8]

Anesthesia:

There are a variety of different classes of anesthetic drugs, many of which act as agonists on the GABA-A receptor, an inhibitory receptor in the brain. Examples of these drugs include the

inhalational anesthetics and propofol (a hypnotic) [9,10,11,12]. These drugs can be used for the maintenance and induction of anesthesia [10]. Anesthetic drug efficacy is measured by its minimum alveolar concentration (MAC), which is the concentration that prevents a muscular response to painful stimuli in 50% of subjects tested. The MAC for inhalational anesthetics is highest at the age of six months and decreases by an average of 6% every ten years [13]. The main inhalation anesthetics currently used are isoflurane, desflurane, and sevoflurane, which are often paired with nitrous oxide to prolong their MAC [14, 15, 16]. Isoflurane has been shown to act on the CA1 and dentate gyrus regions in the hippocampus, areas thought to be involved with spatial sense, memory, and mismatch [11,12,17]. GABA-A inhibition of hippocampal interneuron activity which controls pyramidal activity (voluntary movement) in the cortex and hippocampus was also increased by the presence of isoflurane and sevoflurane [18]. Additionally, isoflurane and propofol were found to decrease glucose metabolism in the brain [19]. The short term effects of these anesthetics on the aforementioned brain regions have been heavily studied; however, long term effects remain to be seen.

Nitrous oxide is the inhalation anesthetic most frequently used in dental practice [20]. It is thought to act on two receptors, the NMDA and AMPA receptors. NMDA is an excitatory ion channel controlled by glutamate and is the most important receptor involved in memory and synaptic plasticity [21]. AMPA receptors are also excitatory and stimulated by glutamate, however in the vertebrate CNS, they are also responsible for the majority of rapid excitatory transmission and they are ubiquitous throughout the CNS [22,23]. Though the mechanism of action of nitrous oxide is not well-defined, it has been found that it can cause a voltage-dependent post-synaptic block of NMDA receptors and a non-voltage dependent block of AMPA receptors [19].

Halothane is an alkyl halide that has been traditionally used as an inhalational general anesthetic. Though halothane is no longer used today because of its cardiotoxic and hepatotoxic side-effects, its impact on the developing brain is still applicable to inhalation anesthetics commonly available due to similarities in its actions. . Halothane is a GABA-A receptor agonist similar to isoflurane, desflurane, and sevoflurane [24]. It has also been found to decrease global glucose metabolism in the brain like isoflurane and propofol [25]. It has also been suggested that halothane and isoflurane have the same binding site at the GABA-A receptor [26].

1.3

Since there is a demonstrated link between general anesthesia and the effect on a developing child's brain, the long term effects on neurodevelopment remain to be fully understood.

2. Objectives:

This systematic analysis sets forth to understand the effect of different types of general anesthesia on the neurodevelopment of children from birth to twelve years old. Neurodevelopment changes were primarily of a learning disability nature and included: linguistic, verbal and mathematic modifications.

3. Methods:

Initially the topic of this paper was "Does general anesthesia adversely affect children's behaviour?" however due to a lack of data and detail, the topic was revised to the current one. For full detail with regards to the methods used in the previous search, please see Appendix I.

3.1 Inclusion and Exclusion criteria

In order to be included in the review, studies had to have been written in English, and carried out on human children (12 years of age and under) undergoing general anesthesia. The title, abstract, and full copy level of elimination were reviewed by five people. For a visual presentation of sections 3.2 to 3.5 please see Table 2 in Appendix II.

3.2 Types of Study Designs

Randomized controlled trials would have been the ideal type of study this paper aimed to review (major limitations), however, case-control studies, and cohort studies were also included. Cross-sectional and case-report studies were excluded.

3.3 Types of Participants

The population included in the search involved children up to and under the age of twelve. Studies that involved children with disabilities for example, Trisomy 21 or Autism, were not selected for inclusion.

3.4 Types of Intervention

The intervention searched for was general anesthesia. Sedation and premedication were excluded.

3.5 Types of Outcome

The studies examined differences in neurocognitive development post-general anesthesia. Neurocognitive development was assessed by judging changes in standardized test scores as compared to average scores (i.e. Wechsler Intelligence Scale, Woodcock-Johnson test, California Achievement Test and Test of Cognitive Skills).

3.6 Search methods for identification of studies

A database search was performed using Ovid Medline (1946 to February week 1, 2012). To supplement the search, Dr. Jason Maynes (a staff anesthesiologist at the Hospital for Sick Children and expert in the field) was consulted after attending a conference on Neurotoxicity and the Developmental Effects of Anesthetics.

3.7 Data collection and analysis

The result of the database search was very specific and therefore a total of seven articles were found based on our new criteria. Every stage of reading was carried out by all five members of the group. Three of the seven were deemed acceptable for critical appraisal. Dr. Maynes indicated to our group that the research in the field was very new (started in 1999 with clinical studies started in 2009), hence the very limited information retrieved using the online databases. Dr. Maynes suggested six articles that were the “gold standard” in the field. Three of which were the articles also found using our online search while the remaining three were generously provided by Dr. Maynes himself.

Therefore, our database search in addition to expert opinion narrowed down the articles to six pieces of literature deemed acceptable for review. These papers were verified against the Causation Checklist described in Table 1. A cutoff score of 9/13 was used in the selection of which paper were justified for use for our systemic review, all of which made the criteria.

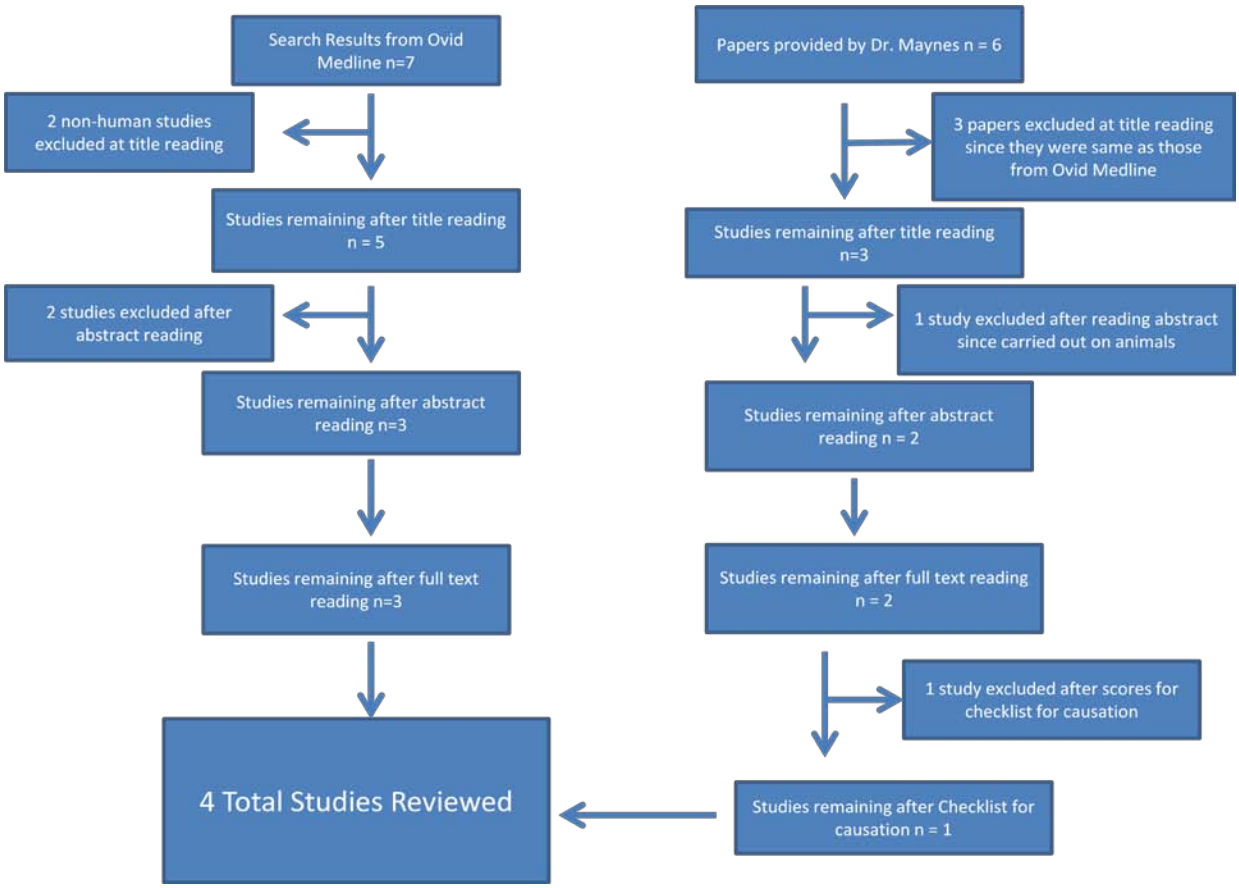
Table 1: Checklist for Assessing Causation
1. Was the study ethical? 2. Was a strong design used to assess causation or risk? 3. Were cases defined validly and reliably measured? 4. Were the risks validly and reliably measured? 5. For diseases with multi-factorial risks, were the risks assessed controlling for other factors and was the model's prediction power strong? 6. Did the "cause" precede the effect? 7. Was the estimate of risk beyond chance and large? 8. Was there a dose-response relationship? 9. Was reversibility demonstrated? 10. Is the "cause" consistently observed in different times, places? 11. Is the "cause" biologically plausible? 12. Is the "cause" specific to that disease? 13. Is the "cause" analogous to another established disease/exposure?

4. Results

4.1 General results of the search

Figure 1 illustrates the general results of the search for studies. Ovid Medline retrieved seven papers, of which two were eliminated at the title stage, and another two at the abstract stage. From the papers provided by Dr. Maynes, three were excluded at the title reading stage as they were identical to three that resulted from the Ovid Medline search. One more study was excluded at the abstract stage and a final study was excluded after the Checklist for Causation stage because it did not meet the scoring cutoff of 9/13. All of the studies used in this review scored between 9 and 10.5 on the Checklist of Causation. Furthermore, all four studies used were retrospective cohort studies.

Figure 1. Flow chart diagram of search process



4.2 Description of studies

4.2.1 Summary of evidence

The studies used were published in either 2009 or 2011 and were carried out in either Rochester Minnesota or New York State, USA. However, two of these studies examined cohorts of subjects born between 1976 and 1982 where halothane was the anesthetic of choice (which is no longer used in practice today). The other two studies examined cohorts born between 1999-2002 and 1999-2005. These studies, although more recent and were more likely to have used relevant contemporary anesthetics, unfortunately did not provide information on the general anesthetics administered.

The participants in these studies were all between the ages of 0 and 4 (two studies looked at children between 0-3 years old, one between 0-2 years old, and one between 0-4 years old). All of these children required an unspecified form of surgery accompanied by general anesthesia. One study specified that the children in the study underwent inguinal hernia repair. All of these studies examined the possible presence of a link between the administration of general anesthesia and the subsequent development of learning, behavioural, or developmental disabilities.

DiMaggio et al. study that examined hernia repair, determined a Cox proportional hazard ratio of 2.3 (95% CI) for the development of a behavioural, developmental, or learning disorder following one administration of general anesthesia [30]. In a follow up study, it was observed that

children who were exposed one time to anesthesia had a hazard ratio of 1.1, those experiencing two exposures had a hazard ratio of 2.8, and those children exposed to three or more was 4.0 (95% CI) [31]. This study also compared siblings that were exposed to anesthesia and those that were not (to further control for confounding variables i.e socioeconomic rearing, home environment) and found that the matched relative risk of a learning disability was 0.9 (95% CI) between siblings [31]. Therefore, while there was no substantial evidence to suggest an increased risk for a behavioural/developmental disorder following general anesthetic in the sibling comparison, a dose-response relationship was seen with multiple exposures of anesthetic in those children that were exposed [31].

Flick et al., 2011 evaluated whether exposures to halothane and nitrous oxide were associated with increased hazard ratios for learning disabilities. This study utilized the California Achievement Test (CAT) and Total Cognitive Score (TCS). It was observed that the hazard ratios for learning disabilities in mathematics with one exposure was 1.08 (95% CI), and with two or more exposures was 2.12 (95% CI). In reading, the hazard ratio for learning disabilities with one exposure was 1.08 (95% CI) and 1.99 (95% CI) with two or more exposures. When evaluating written language learning disabilities, the hazard ratio was 1.09 (95% CI) with one exposure, and 1.88 (95% CI) with two or more exposures. The risk for the subsequent requirement of an Individual Education Plan for speech was 1.21 (95% CI) for one exposure, however with two or more exposures this number increased to 4.76 (95% CI). Therefore this study also presents a dose-response relationship between the number of administrations of general anesthetic and subsequent learning disabilities. [32]

Another study observed an increased risk for learning disabilities with multiple exposures to general anesthetics[33]. One exposure produced a hazard ratio of 1.05 (95% CI), two exposures produced a hazard ratio of 1.78 (95% CI) and three or more exposures produced a hazard ratio of 2.50 (95%CI). Furthermore, multiple exposures and duration of the anesthetic administered increased the risk of developing a learning disability in children.. For example, duration of anesthetic that was below 30 minutes produced a hazard ratio of 0.93 (95% CI) while anesthesia greater than 120 minutes produced a hazard ratio of 1.65 (95%CI). Repeated exposures to anesthetics predisposed 35.1% of patients having learning disabilities by age 19, compared to 20.0% with no disabilities. [33]

Collectively there seems to be a trend in 3 of the 4 studies indicating that multiple exposures of general anesthesia predisposes children to developing learning/behavioural disabilities. Since “increased risk to exposure” is measurable on a scale such that mild risk factor = 1.5, moderate risk factor = 3.0, and strong risk factor = 6.0, the general consensus is that the majority of these studies report that general anesthesia is a “mild - moderate” risk factor for developing learning/behavioural problems in life [34].

Author, Year	Population	Intervention or Test Treatment	Control	Outcome	Critical Appraisal Comments	Conclusion, Strength of evidence & Classification
Wilder et. al, 2009	-Children (M & F), born between Jan. 1, 1976 and Dec. 31, 1982 -Rochester, Minnesota	-n = 593 (single exposure = 449, 2x = 100, ≥3x = 44) -any type of surgery or diagnostic procedure requiring GA from 0-4 years of age	- n = 4764 with no GA	-Learning disabilities were diagnosed using research criteria based on 3 formulas (including the Regression formula-Minnesota)	-Causation checklist score = 10/13 -Anesthetic used was halothane, therefore cannot comment on effects of modern anesthetics -Cannot distinguish between the effects of GA and stress response to surgical injury -Limited generalizability (white, middle class)	**Conclusion:** -Children undergoing multiple administrations of GA before 4 years of age were more likely to develop learning disabilities **Strength of Evidence:** -II-2 **Comments:** - Good study design(retrospective cohort study) - Statistically significant results - Adjusted for most confounding factors
DiMaggio, et. al, 2009	-Children (M & F) in New York State Medicaid program (1999-2002)	-n = 383 (inguinal hernia repair during the first 3 years of life)	- n = 5050 (frequency -matched with no history of hernia repair before the age of 3)	-Presence of a diagnostic code for: unspecified delay or behavioural disorder, mental retardation, autism and language or speech problems	- Causation checklist score = 9/13 - Assumed procedure code for herniorrhaphy indicated exposure to general anesthesia - May be some bias when reporting diagnostic codes for behavioural/developmental disorders - Could not differentiate effects of anesthesia from those of surgery	**Conclusion:** Children under 3 years of age that are subjected to hernia repair surgery are more likely to develop behavioural or developmental disorders **Strength of Evidence**: II-2 **Comments:** - good study design (retrospective cohort study) - statistically significant results - adjusted for most confounding factors
Flick et. al, 2011	-Children (M & F), born between Jan. 1, 1976 and Dec. 31, 1982	- n = 350 (single exposure = 286, ≥2x = 64) - all children who underwent any type of surgery or diagnostic procedure requiring GA from 0-2 years of age	- n = 700 (frequency -matched children that were unexposed to GA)	- Children whom an individualized education program was developed for disorders of emotion/behaviour or for speech/language - Learning disabilities were identified using the results of individually administered tests of achievement - Achievement and cognition assessed using the results of group administered tests (CAT and TCS)	- Causation checklist score = 10.5/13 - Halothane, therefore cannot comment on effects of modern anesthetics - Cannot distinguish between the effects of anesthesia and surgeries - Limited generalizability (white, middle class)	**Conclusion:** -In children between 0-2 years of age multiple administrations of GA were determined to be an independent risk factor for learning development disorders and the institution of an Individual Education Plans for speech (however not for behaviour). Also there was no evidence supporting the idea that individual exposures to GA or surgery were risk factors for the negative outcomes observed. **Strength of Evidence:** -II-2 **Comments:** - good study design (retrospective matched cohort study); statistically significant results - used two methods to control/adjust for health status - looked at multiple outcomes - dose-response effect was demonstrated

DiMaggio, et. al, 2011	-Children (M & F) in New York State Medicaid program (1999-2005)	- n = 304 (children who underwent surgery during the first 3 years of life)	- n = 10146 (random sample of children with no history of hernia repair before the age of 3)	-presence of a diagnostic code for: unspecified delay or behavioural disorder, autism, unsocial and social conduct disorders, developmental delay, reading and language disorders, ADHD and hyperkinetic disorders, and emotional or conduct disorders	- Causation checklist score = 10.5/13 - Good study design (retrospective cohort study) - included a sibling study - no information on the zygosity of the sibling pairs - assumed procedure code for a type of surgery indicated exposure to general anesthesia - may be some bias when reporting diagnostic codes for behavioural/developmental disorders - could not differentiate effects of anesthesia from those of surgery - the database did not include information on the anesthetic used and duration of the anesthetic - difficult to establish causality based on the secondary analysis of observational epidemiological data	**Conclusion:** -In children between 0-3 years of age it was found that there was a 60% greater risk of developing behavioural or developmental disorders when judged against children who did not undergo general anesthesia. **Strength of Evidence:** -II-2 **Comments:** - good study design - statistically significant results - adjusted for most confounding factors

Table 2. Evidence-based table

5. Discussion

5.1

The general consensus of the papers included in this systematic analysis is that there was a dose response dependent risk with general anesthesia administration on the development and behaviour of children. The effects observed are mainly limited to learning disabilities and include: mathematical, written, reading, speech and language deficiencies. The authors noted that the observed changes in neurodevelopment were likely to be caused by the general anesthetic, however, they were unable to differentiate the stress response of the surgery from the anesthesia. The observations were made with children receiving the general anesthesia before the age of four and were more prevalent in males. The types of procedures studied included: herniorrhaphy, appendectomy, tonsillectomy and any surgical or diagnostic procedure involving the use of general anesthesia. The majority of the aforementioned procedures were performed with halothane and nitrous oxide as the main source of general anesthesia. Most of the studies were conducted in the United States and had a sample size ranging from 138 to 593 participants. The children receiving the anesthesia were followed until the age of nineteen. All findings were determined to be statistically significant. External reliability was limited as the studies either looked at children under the United States Medicaid coverage plan (lower income) or of upper class white children, neither of which are generalizable to the entire population. The researchers were unable to establish a dose, duration, type, and route of anesthetic because the databases used for the studies included incomplete records and did not specifically outline the general anesthesia administration. In general, a mild to moderate association was found between general anesthesia and adverse neurodevelopmental effects.

The Bradford Hill criteria for causation are: the strength of association, temporality, consistency, theoretical plausibility, coherence, specificity in the cause, dose response relationship, experimental evidence, and analogy. The studies that were reviewed in this report satisfy some, but not all of the Bradford Hill criteria. Therefore, a causal relationship between general anesthesia exposure during early childhood and adverse neurodevelopment effects cannot be determined.

5.2

Overall this field of research is relatively new and papers started being published in 1999. Due to its novelty, there is only a small sample of research presently available on the effects of general anesthesia and neurodevelopment of children. The majority of the studies were observational influencing their strength of conclusions.

Presently, about one million children under the age of four receive general anesthesia [29]. Understanding the effect of general anesthesia on the development of children in this age range is important as it is within this time that children are most vulnerable to adverse and irreversible effects in neurodevelopment. In procedures that require general anesthesia and are not elective, there is no acceptable alternative to the anesthesia. This research becomes most applicable for elective surgeries whereby general anesthesia is one of the options to treatments. Dentists can utilize general anesthesia or local anesthesia for treatments and thus being up to date with best practice recommendations is essential to provide the most effective and safe treatments for patients.

5.3

All the studies used in the current systematic analysis were retrospective cohort studies which are of relatively strong evidence according to the hierarchy of evidence and are therefore considered to be of good quality. It is unethical to perform randomized control studies in the present field on children and as such, retrospective cohorts remain the strongest possible evidence available.

5.4

There were a few noticeable areas of possible bias in the studies. Firstly, since Medicaid patients were used in some of the studies, a bias existed for under-reporting or over-reporting or duplication of records (for insurance purposes). Secondly, a location bias existed as all the information was extracted from patients living in New York State. Lastly, it is less likely for children with higher medical needs to migrate out of an area receiving adequate Medicaid and as such, a sicker than normal population may have been over-represented.

In addition to bias, there were some limitations that accompanied each of the studies, which would affect their internal and external validity. Firstly, not all the studies reported which anesthetic was used and as well, their dosage and duration were not indicated. The studies that did indicate the type of anesthetic used, relied on halothane, which is no longer widely administered in North America. Therefore, the results of these studies may not be accurately applied to anesthetics that are currently used in practice today. In addition, there was no ideal control group such as children having the medical condition who did not undergo surgery. Stress caused by surgery was not accounted for and may have exacerbated the effects of general anesthesia. One of the major limitations of retrospective cohort studies is that researchers are only able to analyze the data that is collected. In this particular topic, it is feasible to expect a genetic link related to the development of learning disabilities, however, information about learning disabilities present in the family of the children undergoing surgeries was not collected. Information regarding socioeconomic status and education levels of the parents whose children underwent surgery was not collected. Perhaps parents who are in a lower socioeconomic level may be unable to facilitate the education of their children, increasing their susceptibility to developing learning disabilities.

5.5

Throughout the research process, some areas of limitation were determined. Mainly, this field of research is relatively novel and therefore there are a limited number of studies available on the topic. Of the studies available, there are few overlapping researchers who dominate the field, thereby limiting the breadth of expertise. When performing our initial search, we utilized the Ovid Medline research database. Other databases such as Scopus or Google Scholar were available; however, we chose to limit our searches to one database which could have limited our available retrievable articles on the topic. We were also fortunate to speak to Dr. Jason Maynes, an expert in the field to obtain direction and guidance; however, we relied solely on his expertise and did not contact other experts, limiting our outlook on the topic.

5.6

The majority of studies on the topic provided consistent results. The consensus amongst most of the experts in the field is that general anesthesia increases the risk of adverse neurodevelopmental changes in children under the age of four, most prominently seen by the

development of learning disabilities. Bartels *et.al* also conducted a study on 1143 monozygotic twin pairs in the Netherlands and found there to be insufficient evidence for a causal relationship between anesthesia administration and later learning-related outcomes. There was, however, evidence to show that early anesthesia was a marker for an individual's vulnerability towards later learning issues, regardless of their exposure to anesthesia. This study did not specify the drugs administered for anesthesia, nor did it outline the learning-related outcomes. All the studies taken under consideration in this systematic analysis did not find a causal relationship between general anesthesia and neurodevelopmental changes due to confounding variables; however, the majority of them found a mild to moderate association which warrants further research.

5.7

Based on the majority of the presented papers, the authors concluded that there is a mild to moderate association between neurodevelopmental changes in children under the age of four receiving general anesthesia, however at the present time a causal relationship cannot be determined and further research in this field is necessary.

5.8

5.8.1

In non-elective surgeries requiring general anesthesia, the standard of care is to administer the general anesthesia as per the current recommendations. In elective surgeries, however, including some dental procedures, some plastic surgeries, some orthopaedic surgeries or gynaecological procedures, local anesthesia may be deemed as a safer and more preferred alternative, especially in patients under the age of four who are most vulnerable to adverse changes in their neurodevelopment.

5.8.2

Based on the available research, the current best practice recommendation is to avoid using general anesthesia, if possible, on patients under the age of four to avoid any risk of adverse neurodevelopmental changes. Local anesthesia appears to be a safer alternative.

5.8.3

Presently, general anesthesia may only be performed by licensed medical or dental anesthesiologists. Conversely, local anesthesia is administered regularly and routinely by most dentists.

5.8.4

To be able to perform a dental procedure under general anesthesia, greater costs to both the patient and provider are involved. Procedures performed under general anesthesia are generally more costly than their counterpart treatments completed with local anesthetic, thereby increasing costs for the patient. Additionally, more training, equipment, monitors and education is required to administer general anesthesia to patients and therefore increases the costs of the dentist which may later be passed onto the patient.5.8.5

On one hand, the costs per patient and per dentist should decrease if general anesthesia is more readily replaced by local anesthesia as the procedures generally cost less and further

training or equipment is not required. However, more time may be required to work on a child or adult who has difficulty withstanding certain procedures and this would translate into increased costs for the patient and dentist due to increased time for procedure as compared to general anesthesia. The majority of dental treatments are covered through private means, either out of pocket or by insurance and as such there would not be a significant change in cost per population, the changes in cost would be incurred by the individual.

5.8.6

This systematic report brings forth an awareness of the potential effects of general anesthesia to enlighten patients and provide them with a more in depth understanding to be able to make an informed decision regarding their treatment options. Both general anesthesia and local anesthesia are available for certain procedures and therefore current practices are not being altered, rather, best practice recommendations are made according to the specific procedure type and individual undergoing the procedure.

5.9

The studies presently available on the effect of general anesthesia on the neurodevelopment of children have been recent and few in quantity. Research in this field on humans begun in 1999, therefore the body of knowledge should be expanded and broadened to gain a better appreciation of the outcomes assessed. The focus of the studies has been in children up to the age of four as it is assumed that neurodevelopment has matured by that point. However, it is reasonable to assume that neurodevelopment could occur past the age of four due to the differences in environment or genetics. Thus, studies could consider observing effects in children past the age of four. The majority of studies observed the effects of halothane in combination with nitrous oxide on the neurodevelopment of children. Halothane is an outdated general anesthetic and has been substituted by various other types of drugs. As such, it is necessary to examine the effects of the general anesthetics currently used in practice on the neurodevelopment of children. Additionally, it is worth noting that the studies may not have fully considered the implications of anesthesia such as: post-operative recovery times, post-operative cognition, post-operative weakness, prolonged intubation and immune suppression on the neurodevelopment of children. These factors may confound or alter the observed results and should be considered in future research.

It is worth noting that future molecular research is currently being conducted by Dr. Jason Maynes on the topic. His research is currently unpublished and preliminary; however, he consented for it to be described briefly. Dr. Maynes has targeted mitochondria as his first cellular structure of research. He has shown that isoflurane causes a loss of mitochondrial content in the cell with one hour exposure to the general anesthetic. Alternatively, propofol causes a dramatic increase in the mitochondrial content which is similar to what is observed with exposure to hydrogen peroxide, while exposure to morphine does not cause a large change. The changes observed between isoflurane and propofol are likely due to different stress responses, but the mechanisms of action are still being researched. After a four hour period, the mitochondrial content in the isoflurane sampled returned to baseline. Isoflurane was found to cause a dose-response related production in mitochondrial DNA mutations. Isoflurane administered by inhalation, propofol administered by intravenous injection, and administration of morphine were shown to cause gross morphological changes in mitochondria and decreased their functional

capabilities in the cell. Mitochondrial damage may be considered a mechanism by which neurodevelopment changes could occur after the administration of general anesthesia.

A major limitation in the studies was that there were many confounding variables between the control and treatment groups which could have affected the results. Each study compared a surgical treatment group to a non-surgical treatment group. Generally, extensive surgeries are often accompanied with general anesthesia and therefore, the effects of general anesthesia cannot be separately distinguished from those associated with the stress of the surgical procedure. Randomized controlled trials are not a viable option to analyze the question presented in this report as it is unethical to withhold general anesthesia from a patient undergoing surgery for which general anesthesia is indicated. However, future research could be designed to minimize confounding variables. One such research design could include subjects having the same medical condition and requiring the same surgical procedure, however, successful treatment could be performed under general anesthesia or local anesthesia, to obtain the same end result. This study design would eliminate the confounding variable of healthy versus unhealthy. This design could be applied to the dental setting and could be constructed as a randomized control trial for the highest power of evidence. Another study option could include subjects with the same medical condition, however the surgery involved in treatment is elective. For example, patients with enlarged tonsils or deviated septae could be potential subjects for this type of study, as patients could choose to undergo surgery but it is not required for their survival in all instances. A prospective cohort study could be designed in this case, which would eliminate the confounding variables of patients who are more susceptible to effects of surgery and general anesthesia due to their underlying medical condition.

5.10

General anesthesia is an available resource for dental professionals to utilize in more complicated cases as well as for individuals, including children that are unable to otherwise withstand the required treatments with local anesthetics. As such it is pertinent to know all the risks and benefits associated with general anesthesia prior to its application. Patients or legal guardians must be aware of the possible risks that may occur so they can determine with full understanding if they want to proceed with its application. The presented systematic analysis has demonstrated that general anesthesia application has been shown to lead to neurodevelopmental changes as manifested by learning disabilities in children during their period of vulnerability when synaptogenesis is occurring. It is noteworthy to mention that some procedures could not be performed at all or effectively without the usage of general anesthesia; however, it must be made aware to patients and legal guardians that the risk of learning disabilities is higher in children who receive general anesthesia prior to the age of four. The presented research papers also showed an effect of nitrous oxide in combination with halothane, traditional general anesthetic, a commonly prescribed substance by dentists, to have an effect on the neurodevelopment of children. Although, halothane is not commonly used, nitrous oxide is very popular, therefore, its effects must be investigated further to determine its effect with other general anesthetics or by itself on the neurodevelopment of children. The results demonstrate a need for further research in the field to determine best practice protocols.

The current stance by the U.S. Food and Drug Administration (FDA) is that there is suggestive evidence of neurological impairments with general anesthesia administration in children under the age of four, however there is at the present time no recommendation to delay surgeries using general anesthesia[29]. Professionals changing their clinical practices (based on

research that is still premature in its development) would not benefit their patients, as it would take them out of their comfort zone and force them to utilize a new treatment method where they may not be as proficient. This new method that they are inexperienced with may lead to other risks. The FDA has teamed up with the International Anesthesia Research Society to develop a program named SmartTots whose main focus is to make anesthesia safer for children. The group is looking at the effects of anesthesia on children under the age of four as well as the impact of drug types, dosage amounts and number of exposures. Their goal is to determine if any anesthetics are hazardous to children and aim to design a safe anesthetic regime. Many procedures involving children requiring general anesthesia are not elective and therefore should be performed without delay to prevent known adverse effects that would be incurred without the procedure. The dental profession is unique in this field, as it has alternatives to general anesthesia and in many instances can utilize them instead. Dental professionals, if possible under the recommendations by the FDA, should refrain from using general anesthesia for procedures in children under the age of four to minimize neurodevelopmental risks until further and clearer evidence is available.[29]

6

6.1

We would like to thank our tutor Dr. Ihab Suwwan for his guidance and commitment to this project. We would also like to thank Dr. Amir Azarpazhooh for his expertise and support. We would also like to thank Ms. Maria Buda for her assistance in the research searches. Finally, we would like to thank Dr. Jason Maynes for his expertise on the topic and directing us throughout the research process.

6.2

All members of our group worked cohesively on this module. Every group member attended the lecture series at the Hospital for Sick Children. Every member of the group was present and assisted in the research process. All group members contributed equally to the paper and presentation. Corey Ng, Gavin Tse, and Sei Joo Park performed a more in depth analysis of the studies, whereas Teodora Gheorghe played an active role in writing the results section and introduction and Eleanor Weitzner contributed to the introduction and discussion as well as presenting the project on March 9, 2012. Corey Ng and Eleanor Weitzner constructed the abstract. All group members edited and revised the paper together.

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Appendix I – Initial Search

Initial Search Criteria:

The initial preliminary research on the topic "The effects of General Anesthesia on Child Behaviour" required searching the literature for different types of commonly used general anesthetics in the clinical setting. We also evaluated different types of behaviours in order to define specific inclusion and exclusion criteria for our critical appraisal.

Our preliminary findings lead us to consider any type of general anesthesia (i.e. vapor anesthetics and i.v.) and the effect it has on physiological/psychological child behaviours. Prior to searching the online databases, we determined the inclusion and exclusion criteria that would set our boundaries for our PICOS search (Table 2).

Table 3: PICOS Parameters- Inclusion/Exclusion Criteria: The Effects of General Anesthesia on Children's Behaviour.

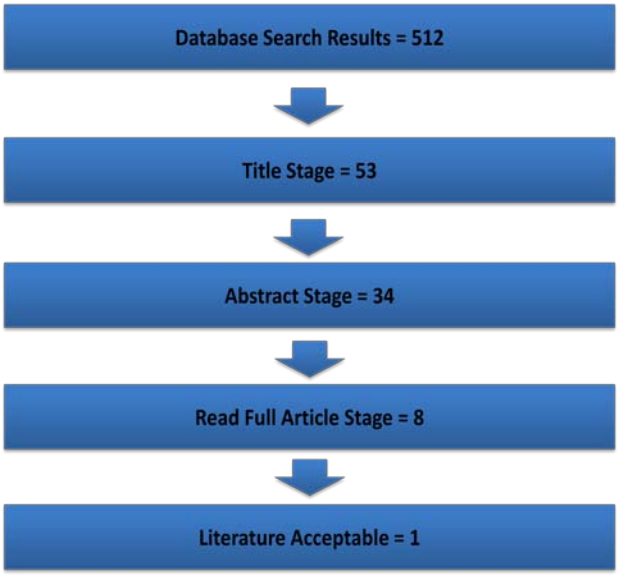
PICOS Category	Inclusion	Exclusion
Population	Healthy children (age≤18) Human English Language	Children (age>18) Children with disabilities (i.e. Autism, Trisomy 21)
Intervention	General Anesthesia (GA)	Non-General Anesthesia (i.e. Conscious Sedation, Premedication
Control	Any GA vs. No GA 1 GA vs. multiple GA	None
Outcome	Psychological, Physiological	
Study Design	RCT, Case-control, Cohort	Cross-sectional, Case-studies

The initial literature search was performed (with professional assistance from the Faculty of Dentistry Librarian) using Ovid Medline (1946 to January week 2, 2012). The subject headings involved keywords: MESH term 1 "General Anesthesia" **AND** MESH term 2 " Behaviour". Both MESH terms were **EXPLODED** and the limitations applied to the search criteria included: English **AND** human subjects **AND** all children (0-18 yrs).

The results of the database search retrieved 512 articles all of which were evaluated by our entire group at the "Title" Stage. Out of the 512 Titles assessed, 53 Abstracts were deemed acceptable however, only 34 of them were accessible via the U of T library system (we therefore did not have access to the other 19 articles for review). The 34 abstracts were divided in half between our group members (17 articles assessed by 2 individuals, 17 articles assessed by 3 individuals) such that abstracts needed to have similar agreement to advance the articles for entire review (8 articles). The 8 articles were further divided (4 articles to 2 individuals, 4 articles to 3 individuals) and a mutual consensus was reached that evaluated only 1 paper appropriate for the critical appraisal.

"The Effects of General Anesthesia on Children's Behaviour"
Ovid Medline Database Search

Figure 2. Flow chart diagram of search process



After thorough assessment and corroboration between group members and instructors, it was deemed necessary to re-evaluate the topic itself since the topic of "Behaviour" was very ill-defined in the context of child behaviour. The problem existed in literature not clearly defining what behaviour was itself. When assessing behaviour, there are a vast number of areas to consider (i.e depression, mood swings, nightmares, crying, delirium etc.) which are difficult to quantify. As such, our "broad" search of "Behaviour" using online databases returned very limited articles that did not specify behaviour in a context that we as a group felt adequate for the purposes of a critical appraisal. We therefore adjusted our topic to include: The Effect of General Anesthesia on Children's Neurodevelopment/Learning

Appendix II – List of potential sources of articles

The subject headings involved keywords: MESH term 1 "Anesthesia" in addition to **EXPLODING** the term and applying "adverse effects" and "methods" as subheadings. MESH term 2 "Developmental Disabilities" was **EXPLODED** and applying "epidemiology" and "etiology" as subheadings. Both MESH terms were combined using **AND** to link them, while applying limitation criteria such as: English **AND** Human **AND** Newborn infants (birth to 1 month) **OR** Infants (1-23 months) **OR** preschool child (2 to 5 years) **OR** Child (6-12 years). The second database search on the new topic: "The Effect of General Anesthesia on Children's Neurodevelopment/Learning" was performed using Ovid Medline (1946 to February week 1, 2012).

Table 4: PICOS Parameters- Inclusion/Exclusion Criteria: The Effects of General Anesthesia on Children's Neurodevelopment/Learning.

PICOS Category	Inclusion	Exclusion
Population	Healthy children (age≤12) Human English Language	Children (age>12) Children with disabilities (i.e. Autism, Trisomy 21)
Intervention	General Anesthesia (GA)	Non-General Anesthesia (i.e. Conscious Sedation, Premedication
Control	Any GA vs. No GA 1 GA vs. multiple GA	None
Outcome	Neurodevelopment	
Study Design	RCT, Case-control, Cohort	Cross-sectional, Case-studies

To further broaden our understanding on the topic of "General Anesthesia and the Effects on Neurodevelopment", our group attended a seminar series on Saturday February 4 at the Hospital for Sick Children. The key speaker of interest was Dr. Jason T Maynes, (a staff anesthesiologist and researcher) and his presentation was: "Neurotoxicity and Developmental Effects of Anesthetics". Being an expert in the field, we were privileged to have had an opportunity to speak with him personally following his presentation. He provided us with several articles to use as well.

Appendix III – Rejection Table

Author & Year	Title	Reasons for Exclusion
Kalkman et al, 2009	Behavior and Development in Children and Age at the Time of First Anesthetic Exposure	Causation checklist score=6/13 It was a pilot study that was conducted to check feasibility of a larger study; Also, the study did not compare children with and without general anesthesia; the results were insignificant
Ikonomidou et al, 1999	Blockade of NMDA Receptors and Apoptotic Neurodegeneration in the Developing Brain	Causation checklist score=5/13 It was a pilot study which looked at the effect of NMDA receptor blockade on developing rat brain; no human subjects involved