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Comparison of hemodynamic stability in moyamoya syndrome patients under mask versus intravenous anesthetic induction

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BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Thesis

**COMPARISON OF HEMODYNAMIC STABILITY IN MOYAMOYA
SYNDROME PATIENTS UNDER MASK VERSUS INTRAVENOUS
ANESTHETIC INDUCTION**

by

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ABSTRACT

Background

Moyamoya syndrome is a chronic and progressive disorder, which affects the cerebral vasculature, especially at the Circle of Willis. Pathologically, the changes occur in the vessel and wall and lead to progressive narrowing and eventual occlusion of the internal carotid artery and possibly additional vessels. As the disorder progresses, decreased cerebral blood flow leads to dangerous ischemic events in pediatric patients, especially transient ischemic attacks and stroke. Surgery is necessary to reestablish proper blood flow however; prior to this a diagnostic cerebral angiogram is performed to visualize the blood vessels affected. During this procedure, intravenous (IV) anesthetic induction is typically used. However, IV access and insertion are likely to agitate children, leading to anxiety and crying. In moyamoya patients, crying and subsequent hyperventilation is a known trigger of ischemic events. Therefore, this study is investigating the safety of mask induction compared to IV for this procedure, which would help avoid episodes of crying.

Methods

Records from moyamoya patients admitted to Boston Children's Hospital for a diagnostic cerebral angiogram during the period of 2007-2013 were analyzed retrospectively (n=98). The main focus was data analysis between patients who underwent IV versus mask induction to determine if there was equivalence of safety based on hemodynamic parameters. An unsafe blood pressure drop is clinically deemed as a 20% or greater drop from the patient's baseline and this criteria was used when determining if a patient was a case (who experienced this unsafe event) or control. (who did not). Additionally, other intraoperative variables were analyzed for possible correlation with hemodynamic stability. Lastly, demographic patient information was gathered to gain an understanding of the population being analyzed. Statistical analysis was performed for all results when possible to determine significance.

Results

In the population analyzed (n=98), n=49 patients underwent IV and n=49 patients mask induction. The proportion of patients who experienced an unsafe drop in blood pressure in both groups was statistically equivalent (p=0.65). Additionally, the difference in magnitude of the average blood pressure drop experienced in case patients was not statistically significant (p=0.07). A significant difference was found between case patients and the groups as a whole for both IV and mask induction. Patients who experienced an unsafe drop in blood pressure had a significantly higher baseline blood pressure (p=0.03, 0.00, respectively). Intraoperative variables analyzed showed no significant correlation to percent blood pressure drop.

Conclusion

The data analysis performed to evaluate hemodynamic safety between IV and mask induction strongly demonstrated that the two methods are statistically equivalent. Based on these results, it is recommended that mask induction be considered an equally safe alternative for anesthetic induction in pediatric moyamoya patients undergoing diagnostic cerebral angiograms, one which may help avoid dangerous ischemic events in the peri-induction period.

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ABBREVIATIONS

ACA	anterior cerebral artery
BP	blood pressure
CSF	cerebrospinal fluid
CT	computed tomography
EPCs	endothelial progenitor cells
ICA	internal carotid arteries
IO	intraoperative
IV	intravenous
MAP	mean arterial pressure
MCA	middle cerebral artery
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
NPO	nothing per oral
P_d	diastolic pressure
P_s	systolic pressure
SD	standard deviation
TIA	transient ischemic attack

INTRODUCTION

Introduction to Moyamoya

Moyamoya syndrome is a rare vasculopathy, which affects the cerebral vasculature. This chronic disorder leads to a progressive occlusion of vessels ultimately requiring surgical treatment. The most serious complications associated with this syndrome include transient ischemic attacks (TIA) and stroke, which occur as a result of decreased cerebral perfusion (Iwama et al, 1996). A physiological response to decreased cerebral perfusion includes the development of a basally located collateral vessel network. This collateral network is a key diagnostic feature of this syndrome in cerebral angiographic findings and has a characteristic appearance of a “puff of smoke”- in Japanese, moyamoya (Smith and Scott 2005).

Terminology to classify moyamoya can be confusing as some terms are used interchangeably. Alone, moyamoya is a term used to describe vascular changes, which are observed in cerebral angiography. The syndrome has a variable presentation pattern and may affect the internal carotid arteries in a unilateral or bilateral fashion, which defines the syndrome and disease, respectively (Smith 2012). However, the presence of bilateral vascular changes in a patient with a well-defined systemic disorder is referred to as moyamoya syndrome.

Moyamoya is a very rare disorder with some patterns of predisposition. It is most common in Japan with a prevalence of 6.03 per 100,000, and also has higher incidence rates in Korea and other Asian countries compared to the rest of the world. (Parray et al., 2011). The disorder is also more common in females versus males with a ratio of 1.8:1.

(Parray et al., 2011). The age distribution of the disorder is bimodal with peaks in the pediatric range at age 5 and in adults at 40. (Ryan et al., 2012) The clinical complications of the disease are variable within these two populations. While the most common serious complications observed in both populations are ischemic events, caused by a lack of oxygen, such as stroke and TIA, the adult population shows a higher frequency of hemorrhagic events, at a rate of 20% vs. 2.8%, respectively. (Parray et al., 2011). The hemorrhagic events are typically linked to the collateral vessel network, which is abnormal vasculature composed of thin and leaky vessel walls (Doi and Kikuta, 2010).

Pathology and Etiology

Moyamoya vascular changes occur at major arteries in the Circle of Willis, a network of arteries, which is basally located and is a major source of the brain's blood supply (Figure 1). Specifically, moyamoya involves a unilateral or bilateral progressive stenosis of the distal portion of the internal carotid arteries (ICA). Additionally, the proximal anterior cerebral artery (ACA) and middle cerebral artery (MCA) are affected to varying degrees (Smith 2012). There are four pathological criteria found in moyamoya syndrome. The first element is the stenosis and eventual occlusion of the lumen in the terminal ICA. Second, similar changes to various degrees are apparent in other arteries of the Circle of Willis, including the ACA, MCA, and posterior communicating arteries. Next, there is the formation and visible appearance of many abnormal small vessels, which form the collateral network, located basally around the Circle of Willis. Lastly,

there are also groups of small vessels observed in the innermost layer of the meninges and the pia mater.

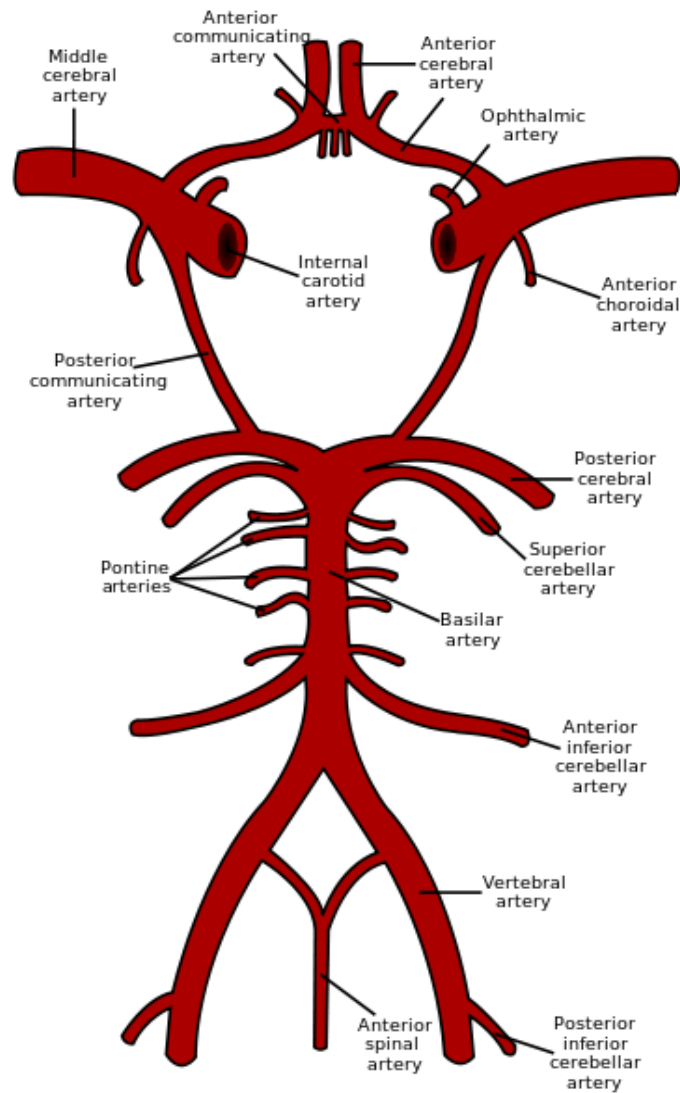


Figure 1. Vessels of the Circle of Willis. This diagram demonstrates the major cerebral vessels which form the Circle of Willis, a major source of the brain's blood supply. Moyamoya changes occur at the terminal internal carotid artery either unilaterally or bilaterally. The adjacent middle cerebral and posterior cerebral arteries may be affected in some cases. (Figure taken from Gray's Anatomy, 37th edition).

Initially, in 1957 moyamoya was classified as a hypoplasia of the bilateral ICA (Doi and Kikuta, 2010). Although the pathogenesis of moyamoya remains unknown, since then, research has progressed and now more detailed studies of the pathology and histology of the disease are available. The primary cause for occlusion of the arterial lumen is a fibrocellular thickening of the intima layer of the vessel wall. Specifically, there is a hyperplasia of smooth muscle cells within the intima. The vessels do not exhibit arteriosclerotic changes or the presence of inflammatory cells. However, in rare cases, lipid deposits may be observed. Other histological characteristics are waviness of the internal elastic lamina and an attenuation of the media layer of the vessel wall (Doi and Kikuta, 2010).

Research has revealed the presence of several markers, which may help elucidate the pathogenesis of moyamoya changes. Although the vessels do not show inflammatory changes, samples of cerebrospinal fluid (CSF) reveal increased levels of vascular-cell adhesion molecule type 1, E-selectin, and intercellular adhesion molecule type-1. The presence of these molecules may indicate an underlying inflammation of the entire central nervous system. (Parray et al., 2011). Additionally, there is an elevated level of fibroblast growth factor in the CSF adding further evidence to the possibility of an underlying systemic process being the cause of the vasculopathy. Lastly, in some moyamoya patients there have been observed similar abnormalities to pulmonary, renal, cardiac and pancreatic arteries. (Smith 2012)

Moyamoya syndrome also leads to vascular abnormalities outside of the Circle of Willis. Most notable is the diagnostic feature of the disease, which is a basally located

collateral vessel network. It is hypothesized that this network forms in response to hypoxic conditions that are a result of ischemia in regions of the brain that are hypoperfused. To support this, research has found an increased number of endothelial progenitor cells (EPCs), which could play a role in angiogenesis of the new vessels. EPCs are stem cells, which are “programmed” to form new blood vessels through angiogenesis and to work in endothelial repair. Unfortunately, the collateral vessels formed in moyamoya patients also have abnormal vessels walls. Contrary to the thickened walls of arteries at the Circle of Willis, the collateral vessels have very thin and leaky walls. This is an underlying cause of hemorrhagic events observed in some moyamoya patients, especially in the adult patient population. For example, the rupture of collateral vessels can trigger an acute subdural hematoma, which is a type of intracranial hemorrhage.

The etiology of the syndrome has yet to be elucidated but it is hypothesized to be of multifactorial inheritance with both genetic and environmental determinants (Smith and Scott 2005). Occurrence in conjunction with congenital disorders, such as Down’s syndrome, supports the hypothesis of genetic determinacy. Also, familial incidence occurs at a rate of 9% - 12% of cases. Genetic studies of moyamoya in Japanese families suggest a link to chromosomes 3, 6, 8, 12, and 17 (Parray et al., 2011). The linkage patterns suggest the disease is inherited in an autosomal dominant manner with low penetrance or in a polygenic manner.

Also, there is strong evidence to support the importance of environmental factors in a multi-factorial inheritance model (Table 1). An example of an environmental

determinant is irradiation; patients who received radiation therapy have a higher risk of developing moyamoya syndrome (Smith, 2012). Additionally, there are case studies of identical twins in which only one twin develops moyamoya, demonstrating that environmental, non-genetic factors play a role in disease development (Smith and Scott, 2005). There are also case reports of patients developing moyamoya syndrome following different infectious diseases (Smith and Scott 2005). As the field of moyamoya research expands and gains awareness, hopefully extended efforts will help answer the questions of etiology so that targets for new treatments can be revealed.

Table 1. Comorbidities associated with moyamoya syndrome. This table depicts various medical conditions, which often coexist in moyamoya cases. Some of the disorders listed have a genetic origin, fueling the hypothesis that moyamoya is a genetic disorder. Others, such as radiation exposure, are environmental factors. (Taken from Smith and Scott, 2012.)

TABLE 1: Moyamoya syndrome—associated conditions*

sickle cell disease
NF1
previous cranial therapeutic radiation
Down syndrome
primary dwarfism
congenital cardiac anomaly
renal artery stenosis
giant cervicofacial hemangiomas &/or PHACE syndrome
hyperthyroidism
Alagille syndrome

* NF1 = neurofibromatosis Type 1; PHACE = posterior fossa abnormalities, hemangioma, arterial lesions, cardiac abnormalities and/or aortic coarctation, and eye abnormalities.

Diagnostic Procedures

If a patient presents with symptoms associated with moyamoya syndrome various tests are conducted in order to confirm the diagnosis. In children, these diagnostic steps typically begin upon presentation with symptoms of an ischemic event such as hemiparesis.

The first step in the workup is a head computed tomography (CT) scan. Signs of stroke in the CT scan include small areas of hypodensity located basally, in ischemic areas of the brain. Also, although rare, CT can reveal evidence of hemorrhage from moyamoya vessels. CT scanning is decreasing in prevalence in many centers, due to concerns for radiation exposure, particularly in pediatric patients.

Next, if there are suggestive findings in the CT scan, a patient will undergo with magnetic resonance imaging (MRI)/magnetic resonance angiography (MRA). Acute infarcts are visualized well using this technique, which is increasingly popular due to its non-invasive nature and lack of radiation. The diagnostic features of moyamoya found using MRI/MRA are diminished flow voids in the internal carotid artery and the anterior and/or middle cerebral arteries. Additionally, prominent collateral flow voids are visualized in the basal ganglia and thalamus regions of the cortex. Experts believe that these findings are virtually diagnostic of moyamoya syndrome.

However, despite the results obtained from MRI/MRA, the invasive cerebral angiography procedure remains the gold standard for both diagnosis and staging of moyamoya (Parray et al., 2011). Angiographic findings are used to confirm the diagnosis of moyamoya syndrome. Also, cerebral angiography is an important pre-operative step

because it allows clinicians to visualize the vessels affected by moyamoya and observe blood flow patterns throughout the brain. Diagnostic findings for moyamoya syndrome in cerebral angiography include terminal occlusion of the internal carotid artery, unilaterally or bilaterally, and also, dilated collateral vessels developed at the base of the brain (Figure 1). The dilated collateral vessel network is what is observed as the “puff of smoke” in cerebral angiography.

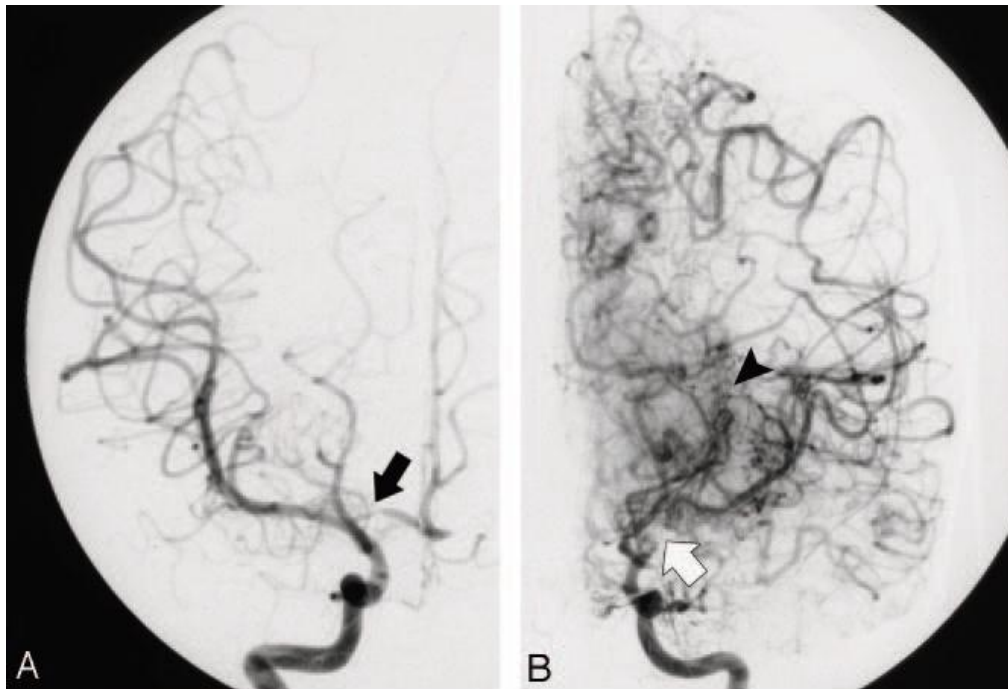


Figure 2. Cerebral Angiography findings in moyamoya patient. This figure shows pre-operative angiographic findings in a moyamoya patient. (A) The right hemisphere cerebral arteries are mostly normal, with some stenosis of the proximal ACA, indicated by the black arrow. No moyamoya collateral vessels are observed. (B) The left hemisphere vessels show significant occlusion, with the white arrow indicating occluded distal ICA and proximal MCA. These findings indicate a Suzuki stage 3. Furthermore, these findings allow clinicians to confirm the moyamoya diagnosis and prepare an operative plan based on the findings. (Taken from Togao et al., 2006)

Additionally, cerebral angiography is necessary to stage the patient's disease and assign a traditionally used Suzuki Stage of 1-6, with a higher stage being correlated to a more severe moyamoya disease state (Table 2). In first stage, occlusion of the internal carotid(s) has begun, however, physiological compensation for this stage has not yet occurred. In the second stage, basal collateral vessels appear in the angiogram. The third stage is a progression of this and is common in diagnosis because at this point there is a prominent basal collateral network, and the likelihood of symptomatic presentation increases. In the fourth through sixth stage there is continued progressive occlusion of the internal carotid(s), culminating in the sixth stages with complete occlusion. A marked feature of the fifth stage is the formation of an extracranial collateral network as a last effort to compensate for the lack of cerebral blood flow.

Table 2. Suzuki Stages of Moyamoya. This table briefly highlights the key features of each stage of moyamoya progression, as defined by Suzuki initially. The findings found using cerebral angiography are the basis for assigning disease grade to a patient. This is one of several reasons that cerebral angiography remains the gold standard and a necessary step in moyamoya diagnosis. (Taken from Parray et al., 2011)

Grade I	Carotid stenosis without collateral vessels
Grade II	Basal collateral vessels seen
Grade III	Prominent basal collateral vessels
Grade IV	Stenotic or occluded circle of Willis and posterior cerebral arteries
Grade V	Extra cranial collateral network
Grade VI	Total carotid occlusion

Adapted with permission from *Arch Neurol.* 1969;20:288–299.

Short-term Treatment Options

Although some medical treatments are administered to moyamoya patients short-term prior to revascularization surgery, none of them are viable solutions because they fail to halt progression or reverse occlusive vascular changes in major cerebral arteries. The lack of non-surgical treatment options is an area that hopefully will be addressed by progress in the research field. Commonly administered medications include blood thinners and antiplatelet agents such as aspirin or ticlopidine. These are administered to help reduce the risk of stroke. Aspirin is dosed based on patient weight and a typical dose in children is 81 mg daily, however, some clinicians prefer to use low-molecular-weight heparin instead of aspirin for antithrombic effects. Low-molecular-weight heparin is also commonly used perioperatively due to its shorter half-life when compared to aspirin. A class of vasodilator drugs known as calcium channel blockers is occasionally used to treat severe headache. However, this class must be used with caution due to its tendency to inducing hypotension, which this patient population cannot tolerate, as it can result in an increased chance of stroke. Other medications may be administered based on a patient's clinical presentation, for example, the administration of anticonvulsants for a patient presenting with seizures.

However, administration of these medications in the absence of surgical treatment is ineffective for moyamoya treatment. The 5-year risk for recurrent ipsilateral stroke is 65% in symptomatic patients with unilateral involvement, and 85% in cases with bilateral involvement when the disorder is not treated surgically. Therefore, to treat the symptoms

of moyamoya and prevent dangerous ischemic events, a surgery is required to increase the brain's blood supply.

Surgical Treatment Options

Ultimately, a revascularization surgery, either direct or indirect, is necessary to re-establish proper cerebral blood flow as the condition is chronic and there is no medical treatment available to reverse or halt its progression (Ryan et al., 2012). The goal of different surgical approaches is the same in that they aim to create a new, effective blood supply to the ischemic cortex. Both approaches use the external carotid circulation as a donor supply for blood vessels because these vessels are not affected by moyamoya. Surgery is recommended as soon as possible after a definite diagnosis has been made in the absence of acute medical complications. The two classes of surgical approaches are direct and indirect revascularizations, with several specific surgeries in each class. Both direct and indirect approaches have shown success with a similar rate and there is no standard procedure. The decision is at the discretion of the surgeon and is based on the patient's age, symptoms, and comorbidities.

Direct revascularization surgery is a type of bypass surgery, which is most commonly used in adults. An example of a direct revascularization procedure is a bypass surgery of the superficial temporal artery to the middle cerebral artery. An advantage of this procedure and other direct surgeries is that there is a subsequent instant improvement in cerebral blood flow. By the same token, however, the sudden increase in blood flow may lead to peri-operative complication such as microbleeds or stroke.

The indirect revascularization surgical approach brings existing richly vascularized tissue in contact with the brain and promotes growth of new blood vessels to increase supply to ischemic areas. This approach is used in the treatment of the majority of pediatric patients. One reason for this is that direct bypass is inherently challenging due to small vessel size in children and the indirect method avoids this problem. Also, angiogenesis appears to be more successful in children when compared to adults. The indirect approach relies on the pro-angiogenic environment of the ischemic brain and encourages the growth of an effective collateral vessel network to increase blood supply. One disadvantage of this approach is that the effects on blood supply are not immediate and it may take months to develop adequate collaterals and provide the intended symptomatic relief.

Anesthetic Considerations for Moyamoya Syndrome Patients

Due to the effects of moyamoya on the cerebral vasculature, the most common and also dangerous manifestation of moyamoya syndrome in pediatric patients is cerebral ischemia. With this knowledge, it is important to take caution in perioperative care of moyamoya patients to avoid events that could trigger an ischemic event. Specifically, efforts should be made to prevent hypocapnea, which leads to cerebral vasoconstriction, and hypotension (Iwama et al., 1996). One precautionary action taken in some cases is the administration of premedication, such as midazolam, to decrease patient anxiety and help avoid crying and subsequent hyperventilation. Additionally, a clinical focus is to

maintain blood pressure near or above the baseline value while the patient is under anesthesia. (Parray et al., 2011).

In pediatric patients one of the major causes of hyperventilation in the hospital setting is crying, and evidence shows that this can increase risk of perioperative stroke (Smith and Scott, 2005). The physiological response to hyperventilation leads to hypocapnea and a cerebral vasculature response of vasoconstriction (Nomura et al., 2001). It is of utmost importance to avoid vasoconstriction in moyamoya patients as their major vessels already have constricted lumens (Parray et al., 2011). Any further constriction could lead to an ischemic complication such as stroke or TIA (Nomura et al., 2001).

Investigating Hemodynamic Stability During Diagnostic Cerebral Angiogram

As discussed previously, before a patient receives a necessary revascularization procedure, he or she must undergo a diagnostic cerebral angiogram to confirm diagnosis and so that physicians may visualize the state of the blood vessel. Currently, there is no standard of care regarding what the best method of anesthetic induction is in this patient population for the cerebral angiography procedure.

Anesthetic induction of patients may be achieved using intravenous (IV) or mask induction. The first option is intravenous induction and may be accomplished with propofol, etomidate, or thiopental, with the most common anesthetic agent being propofol (Parray et al., 2011). The second is mask induction with use of sevoflurane with or without nitrous oxide as an anesthetic agent (Parray et al., 2011). Heretofore the

consensus opinion among anesthesiologists has been that intravenous induction allows for greater hemodynamic stability, a necessity in these patients who cannot tolerate hypotension. However, an advantage of mask induction is that pain and anxiety associated with intravenous line insertion is avoided, making the patient less likely to cry and risk the occurrence of an ischemic event. A case of a moyamoya patient was recorded in which crying during intravenous line insertion led to cerebral infarction and subsequent hemiparesis, which lasted for 3 months (Nomura et al., 2001). This study hypothesizes that mask inductions provide equal hemodynamic stability for moyamoya syndrome patients undergoing anesthesia for pre-operative cerebral angiography anesthesia.

Although moyamoya syndrome is a rare condition, it is relatively common at Boston Children's Hospital due to the pioneering pial synangiosis indirect revascularization neurosurgery developed by Dr. R. Michael Scott. Therefore, a large pool of data is available and this case-series is one of the largest published moyamoya studies. A retrospective study was completed to analyze hemodynamic parameters during pre-operative cerebral angiographies with statistical analysis of mask induction versus intravenous induction groups. Researchers found this study to be necessary so that significant data is available to demonstrate the safety of mask induction for anesthesia for moyamoya patients, especially in children. As explained previously, the disease state of the cerebral vasculature makes patients vulnerable to dangerous ischemic events peri-operatively. Researchers in this study are confident that if mask induction is equally safe to IV induction it should be used preferentially in the pediatric population to help avoid

stress and subsequent crying which is an established trigger for ischemic events in moyamoya patients (Figure 3).

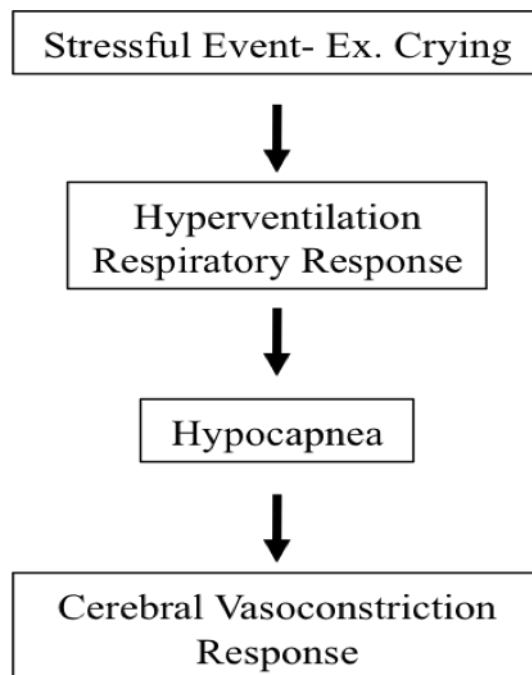


Figure 3. Physiological Response to Crying. This figure depicts the series of events that may happen subsequent to an episode of crying. Although this is non-remarkable in most patients, it may lead to a serious event such as TIA or stroke in a moyamoya patient due to there markedly low cerebral blood flow and basally constricted vessels due to occluded lumens. This study seeks to establish mask induction as an equally safe alternative to IV induction with the advantage of avoiding crying associated with IV usage.

OBJECTIVES

The objective of this study is to determine if anesthetic mask induction and intravenous anesthesia induction result in equal hemodynamic stability in moyamoya patients undergoing cerebral angiography. Our aim is to demonstrate the safety of mask induction in this population, which would allow for this option in anxious or uncooperative children, thus avoiding crying and hyperventilation related to intravenous access. It is critical to avoid hyperventilation in moyamoya patients because it can lead to hypocapnea and a subsequent physiological response of vasoconstriction and decreased cerebral blood flow. Due to the baseline cerebral vascular occlusion in moyamoya patients any trigger of vasoconstriction must be avoided or patients are placed at risk of a further decrease in cerebral blood flow. A further consideration is that a severe drop in blood pressure, which can happen during anesthetic induction can reduce cerebral blood flow, leading to a dangerous ischemic event such as TIA or stroke.

Currently, there is no standard of care for method of anesthetic induction during the necessary diagnostic cerebral angiography procedure for the moyamoya patient population, although informal conversation reveals a prejudice among anesthesiologists in favor of intravenous induction. This procedure is performed prior to the revascularization surgery to visualize occluded vessels and stage the patient's disease. This study seeks to prove that mask induction using sevoflurane is equally safe compared to intravenous induction using propofol for cerebral angiography in moyamoya patients

and to make recommendations towards establishing this method as the standard of care. This hypothesis will be addressed by retrospectively analyzing hemodynamic parameters and perioperative complications in moyamoya patients treated between 2007-2012, grouped by method of anesthetic induction. This study also seeks to create a database of holistic patient data so that more case series may be carried out in the future. Although valuable data such as demographics and patient profiles including comorbidities may reveal interesting trends, the data pool must be larger to draw significant conclusions.

Specific Aims

Determine if mask induction and intravenous induction of anesthesia are equally safe from a hemodynamic perspective for patients with moyamoya syndrome undergoing diagnostic cerebral angiography. This will be accomplished by retrospective analysis of hemodynamic, demographic, and other intraoperative data points during induction period. Hemodynamic data points include: blood pressure measured as mean arterial pressure, heart rate, temperature and end tidal CO₂ during the induction period.

Other data points for analysis include

1. Anesthetic method of induction and drug use
2. Pre-operative administration of midazolam
3. NPO (nothing per oral) time
4. Fluids and blood products administered (cc/kg)
5. Weight (kg)

Demographic data points evaluated include sex, age, race and ethnicity.

The data points referenced above will be used to determine if there is a significant difference in percentage blood pressure drop during the anesthetic induction period.

METHODS

Data Collection

Institutional Review Board (IRB) permission was obtained to retrospectively access medical charts of patients with moyamoya syndrome who underwent diagnostic cerebral angiography prior to pial synangiosis revascularization surgery at Boston Children's Hospital between the years of 2007-2012. Due to the nature of this study, there are no research related interventions or treatments and no identification of individual subjects, therefore, consent was not required from the subjects.

Each patient's medical record was reviewed in a careful and systematic manner. General patient demographic information was gathered including age, weight, race/ethnicity, and existence of comorbidities. Next, the record was searched for a set of preoperative vital signs including temperature, heart rate, and blood pressure. Following this, the anesthesia record of the cerebral angiography procedure was analyzed. Data was collected from the anesthetic induction period of the procedure, which was established after consulting with clinicians as the first 30 minutes of the anesthetic procedure. Data points collected from this intraoperative time period include temperature, heart rate, blood pressure, and end tidal CO₂, NPO time, and fluid and/or blood products administered.

This study's focal point of analysis was blood pressure as a measure of hemodynamic stability. Therefore, two data points measuring blood pressure were collected. First, an average blood pressure throughout the 30-minute induction period and also the lowest blood pressure point during induction was recorded. These values were compared to the patient's baseline blood pressure recorded preoperatively. The data was assessed to see if there was a drop greater than 20% below the baseline blood pressure, a drop of this magnitude is considered clinically significant. This study used the patient's own baseline vitals instead of age-adjusted vital norms for several reasons. First, normalized values are not applicable to the moyamoya population due to their chronic vascular occlusion. As a physiological response, blood pressure may be basally elevated in an attempt to increase cerebral perfusion; therefore many patients may have blood pressures higher than normal. Therefore, a blood pressure drop which would be deemed clinically insignificant when judged on the baseline derived from normal patients could be hemodynamically dangerous in moyamoya patients and lead to dangerous ischemic events. Also, in the operating room clinicians reference the preoperative vital signs when assessing patient progress throughout the procedure, so, this point of comparison was deemed more clinically relevant.

Blood pressure data points recorded on the anesthesia record during the procedure are denoted in the form of systolic/diastolic values. Baseline vitals were recorded as a mix of either mean arterial pressure (MAP) or systolic/diastolic. The value of interest in this study was MAP. Therefore, all blood pressures, which were denoted in the anesthetic record in the form of systolic/diastolic, were then converted to MAP using the

same formula in order to maintain consistency and accuracy. The following standard cardiovascular physiology formula was used for this data conversion (Berne and Levy, 2010).

$$MAP = P_d + \frac{1}{3}(P_s - P_d)$$

Abbreviations:

MAP: Mean Arterial Pressure

P_d: Diastolic Pressure

P_s: Systolic Pressure

After data collection was complete, patients were divided into two groups for analysis based on method of induction, mask or intravenous anesthesia. The key point of analysis was comparing the incidence rate of a blood pressure drop greater than 20% of baseline value. Following this analysis, other variables were assessed in an attempt to elucidate factors contributing or predisposing to potentially dangerous blood pressure drops in moyamoya patients.

Statistics

Power analysis indicated that a minimum of 112 patients in each of the two groups (IV and mask) will provide 80% power to establish equivalence of the incidence of a clinically significant drop of 20% or more in MAP within a clinical margin of 5 mm Hg using a two group test of equivalence of proportions and an one-sided alpha level of 0.05 (version 7.0, nQuery Advisor, Statistical Solutions, Saugus, MA).

Statistical analysis will include univariate comparisons between the IV and mask groups using Student t-test.

Using a drop in MAP of 20% or greater as criteria for assessing safety, we will perform analysis will compare IV and mask routes of anesthesia administration with respect to the incidence of this pre-defined clinically significant decrease in MAP. In addition to analysis of population proportions, magnitude of blood pressure drops will also be analyzed using Student t-test. Lastly, t-test will also be performed to assess differences between the two modes of anesthesia based on the raw data in units of mm Hg. Differences in the incidence of significant drop in MAP will be also evaluated using a 95% confidence interval. Variable data will be analyzed on the bases of population proportions with the Student t-test when the group size (n) allows. Statistical analysis will be performed using SPSS version 19.0 (SPSS Inc./IBM, Chicago, IL).

RESULTS

Population Information

Patient data for all moyamoya syndrome patients undergoing cerebral angiography from 2007-2012 was reviewed. After the pre-operative, diagnostic cases were identified, the total number of patients (n) was 98, divided equally between male and female patients. Lastly, the race/ethnicity of patients was recorded for the patient population (Table 3).

Table 3. Demographics Summary. The table below shows the demographic make-up of the population of moyamoya syndrome patients studied.

Table 3: Demographics Summary		
Sex	n	% of population
Male	49	50.0%
Female	49	50.0%
<i>Total</i>	98	100.0%
Ethnicity	n	% of population
Asian	8	8.2%
Black/African-American	9	9.2%
Caucasian	53	54.1%
Hispanic/Latino	2	2.0%
Other/No Reply	26	26.5%
<i>Total</i>	98	100%

For data analysis purposes, patients were divided into two groups based on anesthetic induction method, either IV induction using propofol or mask induction using sevoflurane. Each of these groups had n=49 patients. In order to assess safety equivalence among the two induction techniques, each patient was evaluated and classified as either a case or a control based on blood pressure. In order to be a case, the patient's average mean arterial pressure during the anesthetic induction period dropped from their pre-operative baseline by more than 20%. In the IV group (n=49) there were 35 control patients and 14 cases. In the mask group (n=49), there were 37 controls and 12 cases (Table 4).

Table 4. Data Summary. The table below summarized the patient population analyzed in this study. Additionally, it shows how many patients were the groups being evaluated, controls versus cases. Case patients underwent an unsafe blood pressure drop (greater than 20% drop from baseline) during the anesthetic induction period.

Table 4: Data Summary				
Induction Method	Anesthetic Agent	Total	Controls	Cases
IV	Propofol	49	35	14
Mask	Sevoflurane	49	37	12
<i>Total</i>		98	72	26

Equivalence of Safety Assessments

In order to determine equivalence of safety based on the occurrence of cases in each group, the proportion of patients that dropped over 20% from their baseline blood pressure was determined (Table 5). Additionally, the cases were evaluated to determine on average how large the blood pressure (BP) drop was. When analyzing the IV

induction group (n=49), the rate of occurrence of cases was 28.6% (Figure 4). On average, the cases experienced a drop of 25.9% from baseline MAP during the induction period, with a standard deviation (SD) of 12.1% (Table 5, Figure 5). Next, when analyzing the mask group (n=49), the rate of occurrence of cases was 24.5% (Figure 4). On average, the cases experienced a drop of 30.3% from baseline MAP during the induction period, with a standard deviation of 6.7% (Table 5, Figure 5). The rate of occurrence of cases in the IV group versus mask group was statistically insignificant as measured by a p value of 0.65. Additionally, the average blood pressure drop experienced by patients in the IV versus mask induction group was also not statistically significant with a p value of 0.07.

Table 5. Occurrence of Cases by Average Intraoperative Induction BP. This table shows a summary of case incidence in the two groups analyzed as well as the average BP drop experienced. The p values were derived from a t-test and showed not statistically significant difference between the two groups for rate of occurrence or average BP drop.

Table 5: Occurrence of Cases by Average Intraoperative Induction BP				
Group	Rate of Occurrence	Avg. BP Drop	SD	
IV/Propofol	28.6%	25.9%	12.1%	
Mask/Sevoflurane	24.5%	30.3%	6.7%	
	p=0.65	p=.07		

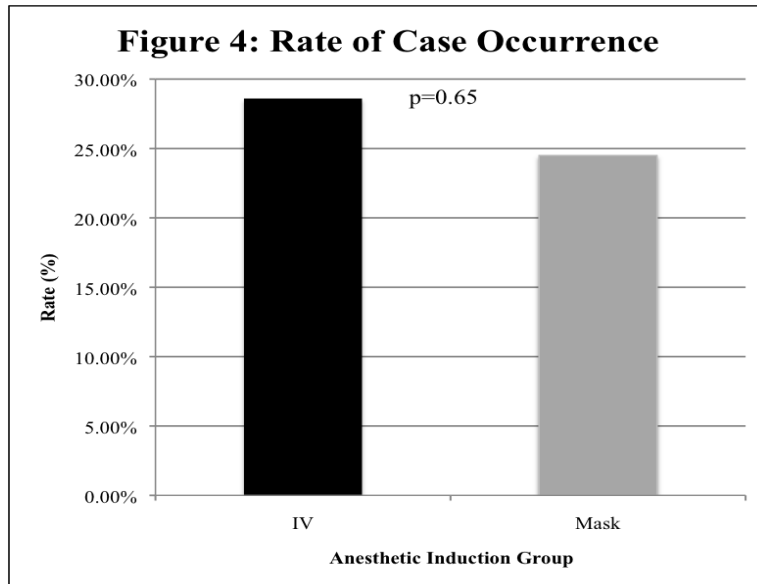


Figure 4. Rate of Case Occurrence. This figure shows the rate of case occurrence based on average blood pressure drop during anesthetic induction period. There was no significant difference between IV and mask induction ($p=0.65$).

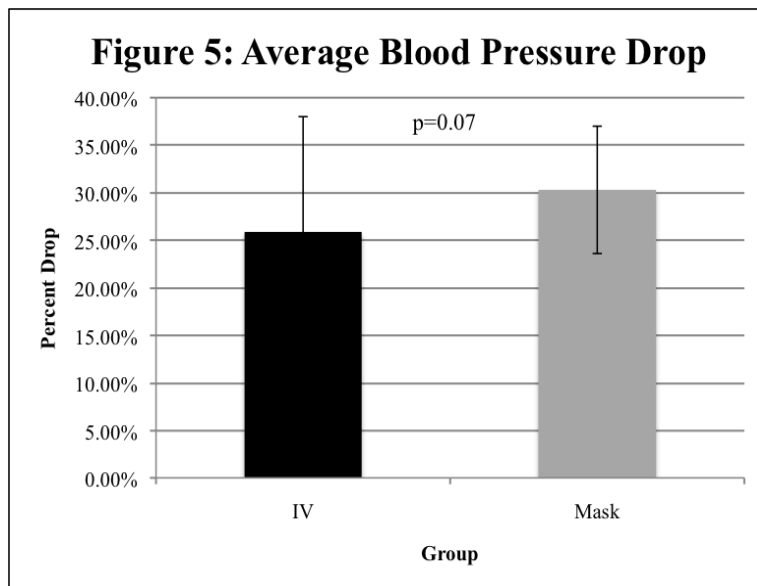


Figure 5. Average Blood Pressure Drop. This graph shows the difference in the average blood pressure drop during the anesthetic induction period in patients under IV versus mask induction. No significant difference was found ($p=0.07$), and therefore, statistically the blood pressure drops can be interpreted as equal amongst the two patient populations.

To further investigate equivalence of safety, a second type of case was defined. For this instance the definition of a case was if the single lowest recorded blood pressure point during the induction period, instead of the average, was 20% or more below the baseline blood pressure. When assessing groups for this type of case, the rate of occurrence in the IV group was 59.2% versus 53.1% in the mask group. This difference was not statistically significant as measured by a p value of 0.54. On average, the IV group cases' lowest blood pressure point was 29.9% lower than baseline with a standard deviation of 6.4% and the mask group cases were 31.9% lower than baseline with a standard deviation of 10.1% (Table 6). The difference in magnitude of the average BP drop was also not statistically significant, measured by a p value of 0.57.

Table 6. Occurrence of Cases by Lowest Blood Pressure. This table shows analysis based on lowest single blood pressure during induction period. Again, there was no significant difference in rate of cases or in the magnitude of average BP drop between the IV and mask groups.

Table 6: Occurrence of Cases by Lowest Blood Pressure			
Group	Rate of Occurrence	Avg. BP Drop	SD
IV/Propofol	59.2%	29.9%	6.4%
Mask/Sevoflurane	53.1%	31.9%	10.1%
	p=0.54	p=0.57	

Lastly, after analyzing the data based on proportions, the groups were evaluated using the raw blood pressure data based on MAP as measured in units of mm Hg. First, each group, IV and mask, was evaluated as a whole. The IV group (n=49), had an

average baseline MAP of 79 mm Hg. The average MAP during the intraoperative induction period was 69 mm Hg and therefore an average drop of 10 mm Hg (Figure 6). The mask group (n=49) had an average pre-operative baseline of 78 mm Hg, average induction BP of 69 mm Hg, and therefore, an average drop of 9 mm Hg (Figure 6, Table 7). The groups as a whole showed no statistical difference in baseline or average intraoperative induction period BP with p values of 0.64 and 1.00, respectively.

Next, the cases in which the average MAP during the intraoperative induction period dropped 20% or more from baseline were also evaluated using raw data. The IV group cases (n=14), had an average baseline MAP of 84 mm Hg and subsequent average induction period MAP of 62 mm Hg. Therefore, on average, IV cases dropped 22 mm Hg from their baseline blood pressure (Figure 7). The mask cases (n=12), had an average baseline MAP of 85 mm Hg, average induction period MAP of 59 mm Hg, and therefore, average MAP drop of 26 mm Hg (Figure & Table 7). Again, the IV versus mask cases showed no statistically significant difference in baseline or average intraoperative induction period BP as measured by values of 0.8 and 0.46, respectively.

Table 7. Blood Pressure Data Summary- in mm Hg. This table shows analysis based on raw data for MAP in mm Hg. Key data points were the average baseline MAP and average IO MAP. Statistical analysis and p values are based on t tests performed.

*IO- intraoperative induction period

Table 7: Blood Pressure Data Summary- in mm Hg							
<i>All patients</i>							
Group	n	Avg. Baseline MAP	SD	Avg. IO* MAP	SD	Avg. MAP Drop	
IV/Propofol	49	79 mm Hg	11	69 mm Hg	10	10 mm Hg	
Mask/Sevoflurane	49	78 mm Hg	10	69 mm Hg	10	9 mm Hg	
		p=0.64		p=1.0			
<i>Cases</i>							
Group	n	Avg. Baseline MAP	SD	Avg. IO* MAP	SD	Avg. MAP Drop	
IV/Propofol	14	84 mm Hg	12	62 mm Hg	13	22 mm Hg	
Mask/Sevoflurane	12	85 mm Hg	7	59 mm Hg	5	26 mm Hg	
		p=0.8		p=0.46			
<i>All patients v. Cases</i>							
IV/Propofol		p=0.03					
Mask/Sevoflurane		p=0.00					

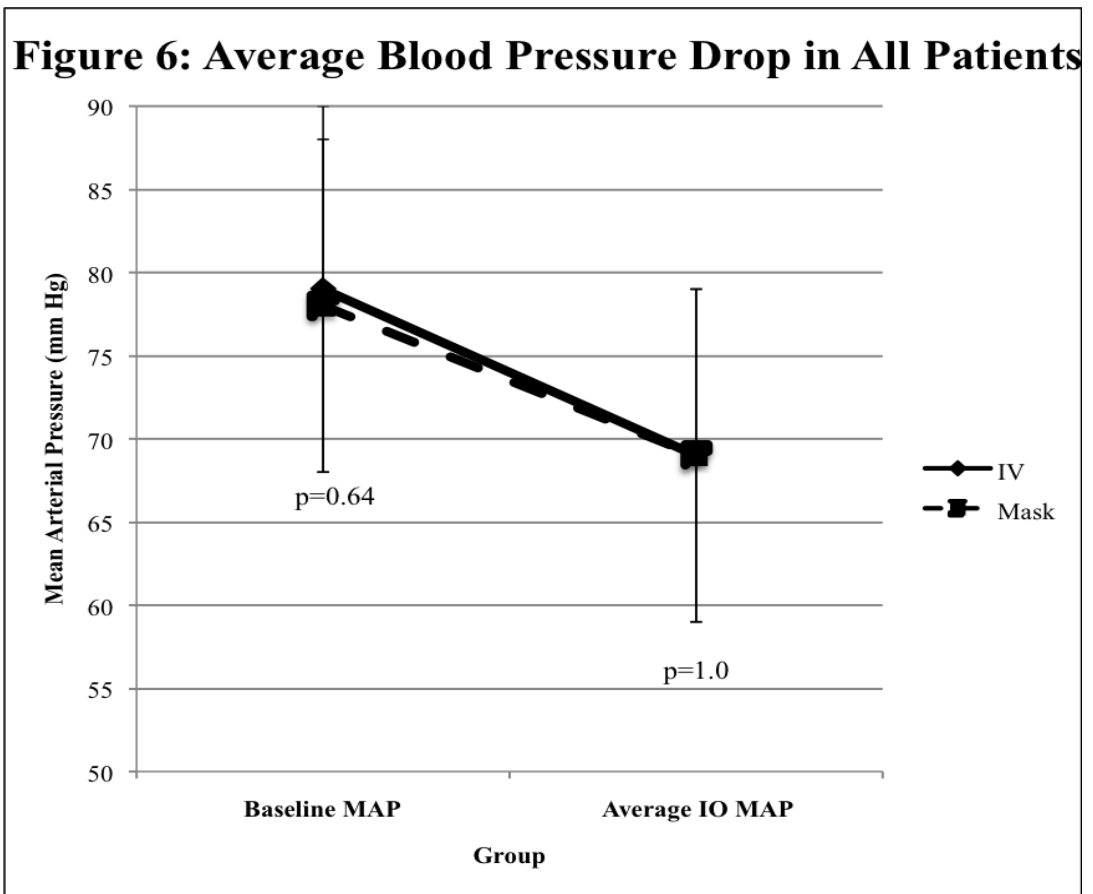


Figure 6. Average Blood Pressure Drop- in mm Hg. This graph depicts the average blood pressure drop experienced between baseline point and induction period in the IV versus mask group. There was no statistically significant difference at either point ($p=0.64, 1.0$)

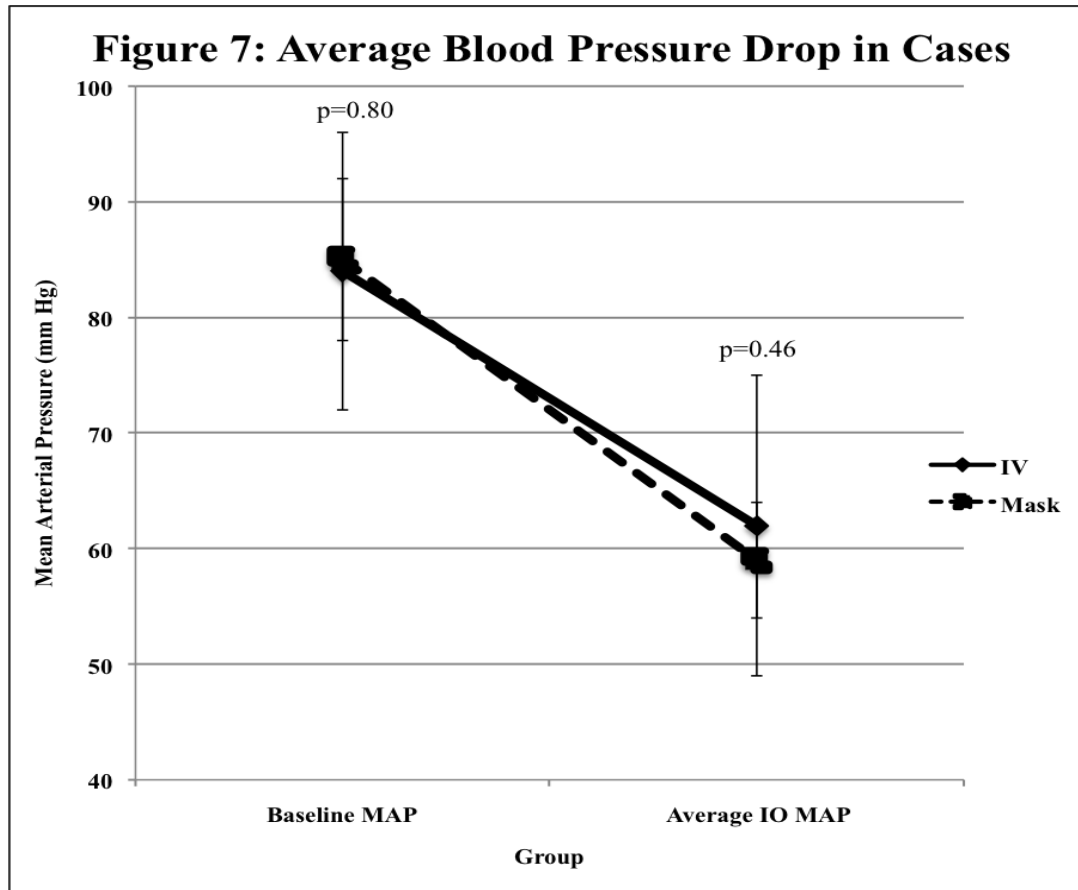


Figure 7. Average Blood Pressure Drop in Cases. This graph depicts the average blood pressure drop experienced between baseline point and induction period in the IV versus mask group when solely analyzing case patients. There was no statistically significant difference at either point (p=0.80, 0.46).

Interestingly, when comparing IV induction case patients versus the IV group as a whole, there was a significant difference in baseline MAP. Patients who were cases and therefore experienced an unsafe BP dropped had an average baseline BP of 84 mm Hg compared to 79 mm Hg for the group as a whole. This was deemed significant by a p value of 0.03. In mask cases versus the whole group there was also a significant difference with a p value of 0.00 (Table 7).

Variable Analysis

During data collection, variables in addition to hemodynamic data were collected and analyzed for possible correlation in control patients versus case patients who experienced what is clinically deemed as an unsafe blood pressure drop.

First, the patient data was grouped by age into two groups. The first group was patients less than 10 years old and there were 69 patients in this group. Of the 69 patients, 23 underwent IV and 46 underwent mask anesthetic induction. The next group was patients 10 years old or older, and this group had 29 patients. Of the 29 patients, 26 underwent IV and 3 underwent mask anesthetic induction (Table 8).

Additionally, the cases in which average intraoperative induction period MAP dropped by 20% or more from baseline were also grouped based on patient age. When analyzing case patients under the age of 10 (n=15), the rate of occurrence of cases was 21.7% when using both IV and mask induction. In total, 57.7% of cases occurred in patients under the age of 10. In case patients 10 years old or older (n=11), the rate of occurrence of cases was 34.6% under IV induction and 66.7% under mask induction. In total, 42.31% of all cases occurred in patients 10 years old or older (Table 8). Based on

t-tests, the difference in rate of cases when IV induction used in younger versus older children was not statistically significant, measured by a p value of 0.32. This analysis could not be performed for mask induction because in older children the sample size was too small (n=3). Additionally, the rate of cases, regardless of induction method, was not statistically different in older versus younger children as measured by a p value of 0.26.

Table 8. Data Summary by Age Group. This table shows analysis when the patient population was separated into two age groups, under 10 years old and 10 years old or older. Furthermore, the age groups were also analyzed based on anesthetic induction method.

Table 8: Data Summary by Age Group						
<i>Summary</i>						
Age	n	IV	Mask			
< 10 years old	69	23	46			
≥ 10 years old	29	26	3			
<i>Cases</i>						
Age	n	IV	Rate	Mask	Rate	Total Rate
< 10 years old	15	5	21.7%	10	21.7%	57.69%
≥ 10 years old	11	9	34.6%	2	66.7%	42.31%
			p=0.32		p=n/a	p=0.26

The next variable analyzed was whether or not an anti-anxiety premedication, Midazolam, was administered prior to anesthetic induction. Out of the entire patient cohort (n=98), Midazolam was administered to 49 patients, or 50%. In patients undergoing IV induction (n=49), the premedication was administered 69.4% of the time, and in patients undergoing mask induction (n=49), it was administered 30.6% of the time.

Next, only the cases were analyzed for administration of Midazolam. When looking at all cases (n=26), regardless of induction method, 11 (or 42.3%) of patients did receive Midazolam, and 15 (or 57.7%) of case patients did not receive Midazolam (Table 9). Statistically speaking, there was no difference in rate of occurrence of patients between the group that did receive the premedication Midazolam and the group that did not (p=0.27).

Table 9. Midazolam usage. First, this table shows the rate of administration of Midazolam in patients induced using IV and mask methods. Next, it analyzes the rate of administration in all cases, regardless of induction method. There was no significant difference in occurrence of cases when Midazolam was/was not administered.

Table 9: Midazolam Usage		
<i>In all patients</i>		
IV/Propofol	34	69.40%
Mask/Sevoflurane	15	30.60%
<i>In all cases</i>		
yes	11	42.30%
no	15	57.70%
		p=0.27

Additionally, administration of nitrous oxide during anesthetic induction was also analyzed. Of the entire patient cohort (n=98), it was administered to 51 patients. Of patients who received nitrous oxide (n=51), 13 (or 25.49%) were cases in which the average intraoperative induction period blood pressure dropped 20% or more from baseline. Of patients who did not receive nitrous oxide (n=47), 13 were cases (or

27.66%) (Table 10). Statistically speaking, administration of nitrous oxide had no significant effect of the rate of case occurrence, measured with a p value of 0.81.

Table 10. Nitrous Oxide Usage. This table first shows the number of patients who did/did not receive nitrous oxide during anesthetic induction. Additionally, it shows the number of cases and the corresponding occurrence rate of cases, which was not significantly different based on administration of nitrous oxide.

Table 10: Nitrous Oxide Usage			
Usage	Total	Cases	Rate
Yes	51	13	25.49%
No	47	13	27.66%
			p=0.81

Also, the variable of nothing per oral time (NPO) was analyzed. NPO is defined as the number of hours prior to the surgery in which the patient has had no food or drink. The patient cohort was analyzed as a whole to assess if there was a correlation between the number of NPO hours and the percent change in blood pressure as compared to baseline. When plotted, the data revealed that there was no correlation ($R^2=2E-05$) between these two data points (Figure 8).

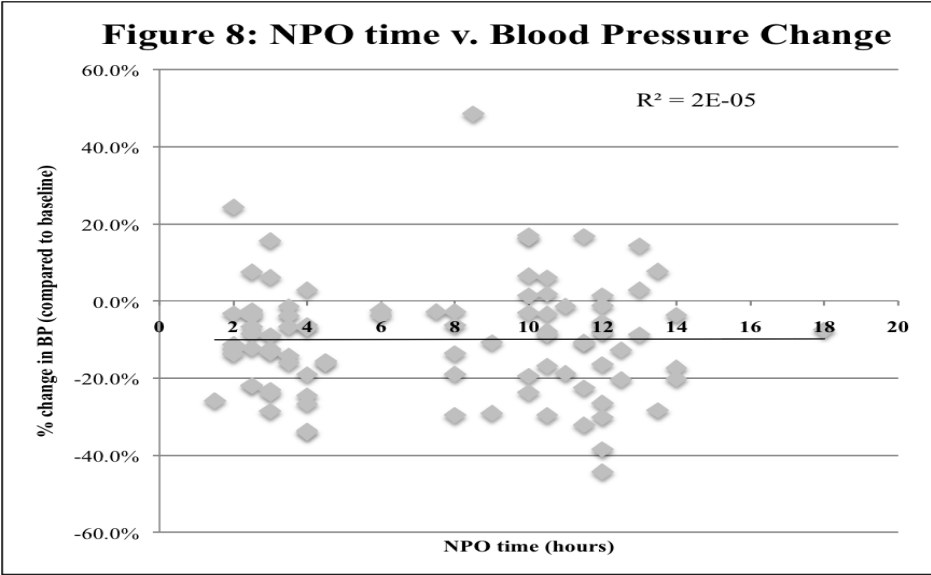


Figure 8: NPO time v. Blood Pressure Change. This scatter plot shows that no correlation between NPO time and percent change in blood pressure was found.

Lastly, the patient records were reviewed to find the existence of comorbidities, chronic conditions experienced by the patient in addition to moyamoya syndrome. Of the 98 total patients, 25 had an existing comorbidity and 73 did not. The rate of occurrence of cases in patients with comorbidity was 36% versus 23.3% in patients with no other chronic illness. The specific illnesses were also noted (Table 11), and they overlap with the conditions cited in literature (Table 1) as common comorbidities in moyamoya patients. Although this data is noteworthy, it could not be evaluated statistically due to the small sample size.

Table 11. Incidence of Comorbidities in Patients. This table shows the number and corresponding rate of case occurrence in patients when grouped based on the existence of a chronic comorbidity. Also, it shows the frequency of the most common comorbidities observed in the patient cohort.

Table 11: Incidence of Comorbidities in Patients			
Classification	Total	Cases	Rate
Existing Comorbidity	25	9	36%
No other illness	73	17	23.3%
<i>Specific Comorbidities</i>			
Down's Syndrome	4	2	50.0%
Irradiation Exposure	11	4	36.4%
Neurofibromatosis Type 1	1	1	100.0%
Sickle Cell Anemia	8	1	12.5%
Von Willebrand Disease	1	1	100.0%

The results obtained in this study allowed for a multi-faceted evaluation of clinical safety associated with different induction methods in moyamoya syndrome patients. Moving forward, the results have important implications in regard to the care and treatment of these patients.

DISCUSSION

Results

The key data analysis in this study involved evaluating equivalence of safety assessments for IV and mask anesthetic inductions in moyamoya patients undergoing diagnostic cerebral angiograms. This was the key aspect of this study and therefore was studied from different approaches to ensure that it was equally safe from every perspective.

First, this was analyzed by comparing proportions of the patient populations that were deemed “cases” due to an average induction period blood pressure drop of 20% or greater from their baseline blood pressure. This comparison showed that the proportion of cases in IV and mask induction groups was statistically equivalent. Furthermore, to ensure that something was not missed, a second class of case was devised. This time, patients were labeled as “cases” if their single lowest blood pressure point, instead of average, during the induction period dropped 20% or more from baseline. Again, the proportion of patients in the IV versus mask group who experienced this clinical event was statistically equivalent.

Following evaluation based on patient proportions, the raw data for blood pressure points in units of mm Hg was analyzed. Again, the data for IV versus mask groups was proved to be statistically equivalent. One statistically significant difference was found, however. For both IV and mask groups, patients who were cases based on average blood pressure drop had a significantly higher baseline blood pressure when

compared to the IV and mask groups as a whole. Although initially counterintuitive, this intriguing result reveals something noteworthy. The patients who experienced unsafe hemodynamic changes during anesthetic induction had on average, a significantly higher baseline blood pressure. This could indicate that their moyamoya syndrome was more advanced and a physiological compensation of increased blood pressure was occurring. Moving forward, it would be valuable to research the Suzuki stage of each patient and search for a possible correlation between stage and blood pressure drop.

Conclusively, all equivalence of safety assessments demonstrated that mask is equally safe to IV induction as measured by blood pressure drops during the anesthetic induction period. Based on this study's hypothesis being proven, it is recommended that mask induction be considered equally safe and potentially preferable for moyamoya patients undergoing diagnostic cerebral angiograms.

In addition to safety assessments, different operative variables were analyzed. Of the variables analyzed, none were shown to have a statistically significant effect on the magnitude or frequency of average blood pressure drop during the intraoperative anesthetic induction period. These variables included age, midazolam usage, nitrous oxide usage, NPO time, and existence of a chronic comorbidity. Some of these variables could not be assessed for statistical meaning due to small sample sizes, and this is an example of something that could be addressed in the future.

Future Directions

The main source of limitation in this study was a small patient cohort (n=98). Despite being one of the largest case series studies on moyamoya patients, the small number of patients made some statistical analysis impossible to perform. For example, a power analysis could not be performed because this would have required a patient cohort of 224 patients for 90% power. Additionally, as noted in the results, when analyzing based on age group, t-test could not even be performed for the mask induction patients due to small sample size.

Moving forward, maintaining the current data set and enrolling additional patients as they are seen at Boston Children's Hospital is the best strategy. Eventually, enough data will be available to surpass the current limitations on analysis. An interesting part of analysis that could not be statistically evaluated was the rate of occurrence of cases based on the presence or absence of a chronic comorbidity in addition to moyamoya. Future analysis of these patients is essential because if a trend in anesthetic safety is found it would be feasible to set the standard of care for patients with moyamoya and comorbidity "X".

For now, knowing that mask induction is equally safe to IV induction for diagnostic cerebral angiograms is very important and it is hoped that future studies may reveal more data trends that can improve the care of moyamoya patients.

CONCLUSION

In conclusion, the hypothesis behind this study was proven to be correct in that mask induction is a statistically proven, equally safe method for anesthetic induction when compared to IV induction when moyamoya patients are undergoing diagnostic cerebral angiograms. Due to the hemodynamic complications that could possible arise due to crying and anxiety associated with IV insertion and access in pediatric patients, this study strongly recommends that mask induction be considered equally safe and possibly preferential to IV for this patient population during this specific procedure.

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