COLLEGE OF MEDICINE AND HEALTH SCIENCES

DEPARTMENT OF SURGERY

NEURO SURGERY UNIT

PROPOS AL ON INCIDENCE AND PREDICTORS OF SURGERY RELATED CEREBRO- VASCULAR ISCHEMIC COMPLICATIONS AMONG PATIENTS UNDERGOING CRANIAL NEURO-ONCOLOGIC PROCEDURES: MULTI-CENTRIC PROSPECTIVE OBSERVATIONAL STUDY

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Acronyms and Abbreviations

EBI

DCI

TCD

Cerebral blood flow velocities (CBFV)

CVS: cerebral vasospasm

Summary

Background: Surgical management of brain tumors while proved to be the single most effective therapeutic armamentarium; it is not however free of some dreadful complications like cerebrovascular ischemic complications. These ischemic cerebrovascular complications are separate entities of variable severity of basically the same problem; an ischemic vascular problem ultimately resulting cerebral infarction and /stroke with significant morbidity and mortality to the patients. This surgery related cerebrovascular problem comprises of a spectrum of disease entities that includes cerebral vasospasm, delayed cerebral ischemia (DCI), vascular thrombosis, pseudoaneurysms, direct iatrogenic vascular injuries and ischemic &/embolic strokes with different diagnostic modalities, therapeutic options and outcome.

Objective: The main objective of this study will be assessing the incidence and predictors of surgery related cerebro-vascular ischemic complications among patients undergoing brain tumor resection at BLH & MCM from April 1-September 30; for 6 months. In addition, this study will also be developing a risk prediction model for the prediction of cerebral vascular ischemic complications among the study subjects.

Methodology: A hospital based prospective observational cohort follow-up study will be conducted starting from April 1-September 30 for the occurrence of ischemic cerebral vascular complications among patients who underwent cranial surgery for brain tumor resection. The study outcome will be assessed in patients who underwent brain tumor surgery at the immediate postop, 3-4th post op day, 7-8th post op day, 12-14th post op day and 30th postop day based on a set of diagnostic criteria and operational definition set. Univariate & bivariable analysis will be done to see the association of each predictor variable with cerebral vascular ischemic complication. Variables with p-value of <0.25 in the bivariable analysis will be entered to multivariable analysis. The statistical significance will be declared at p-value <0.05. The measure of association will be Risk Ratio (RR) with 95% confidence interval. The risk prediction model will also be presented in the form of nomogram.

Conclusion: post cranial tumor resection cerebrovascular ischemic complications are grave complications that have immense implication to the patient's overall functional outcome. Hence, this problem warrants study.

1. Introduction

1.1.Background

Neuro-oncologic diseases are common pathologies that affect brain. This neuro-oncologic problem encompasses a multitude of variable brain tumors affecting different parts of brain with different treatment options and outcomes. Despite there are multimodality treatment strategies, surgery remains the most effective and mainstay of treatment to most brain tumors regardless of tumor histologic type. This doesn't underscores however that surgery is the only treatment as non-surgical modality treatments also had crucial adjuvant therapeutic role; altogether improving patients long survival and quality of life. Each therapeutic option has their own pros and cons, including loss of life from therapy related complications. Surgical management of brain tumors while proved to be the single most effective therapeutic armamentarium, it is not however free of some minor and dreadful complications. Cerebrovascular ischemic neurologic complications are one of the important complications. Though ischemic neurologic complications are described as rare complications in literatures, it is still one of the common life threatening and dreadful complications that contributes to significant morbidity and mortality of patients. Surgery related cerebral Ischemic complication in itself comprises of a spectrum of disease entities that includes cerebral vasospasm, delayed cerebral ischemia (DCI), vascular thrombosis, pseudoaneurysms, direct iatrogenic vascular injuries and ischemic &/embolic strokes with different diagnostic modalities, therapeutic options and outcome. [1]

Though neuro oncologic procedures have been practiced since 2010 in our setting and there were many studies carried out to assess some of the surgery related complications, there has never been an effort made to study about the ischemic complications of brain tumor surgery. Hence, this study will try to study the prevalence, predictors and outcomes of ischemic cerebrovascular complications among patients undergoing brain tumors surgery in two of Addis Ababa University affiliate teaching hospitals: Black Lion Hospital (BLH) and Mysung chrstian Medical Hospital (MCM).

1.2.Statement of problem

Surgery related cerebral ischemic complications are common dreadful complications that result as unwanted complications of brain tumor cranial surgery. This complications encompasses cerebral vasospasm, delayed cerebral ischemia (DCI), vascular thrombosis, pseudo aneurysms, direct iatrogenic vascular injuries and ischemic &/embolic strokes.[1] These spectrums of ischemic complications are extremely important as they add significant morbidity and mortality to patients' outcome. There exists paucity and significant variability of the available evidences in this regard. Not only this, there is also non standardized ways of diagnosing this separate entities of variable severity of basically the same problem; an ischemic vascular problem. In addition, the methodologies used by most available studies are retrospective in nature and full of methodological biases. Similarly, nearly half of the studies are done with small cases of patients. Last but not least is that, this grave complication of brain tumor surgery has never been studied in our setting where brain tumor surgery has routinely been performed since 2010 and significant number of patients ended up with significant morbidity and mortality. Furthermore, there is lack of uniformity in the workup and diagnosis of patients with these complications. This in turn contributes to missed , wrong or delayed diagnosis, which ultimately puts the patients' life at risk of sever morbidity and mortality as appropriate and targeted therapy will not be given.

In general, because of the afore mentioned rationales, the incidence, predictors for occurrence and outcomes of ischemic cerebral complications are lacking in our setting in particular and in the existing literatures in general. Besides, there is no a risk prediction model used for the early identification of high risk groups developed in our setting so far. Hence, this study will be addressing the main limitations of our setup & previous studies by conducting this prospective observational research in a fairly large number of patients.

1.3.Literature review

Cerebrovascular ischemic complications following cranial tumor resection surgery is one of the sever life threatening complications and this incorporates a spectrum of cerebral vascular ischemic insults including angiographic cerebral vasospasm, clinical cerebral vasospasm or delayed cerebral ischemia (DCI), delayed cerebral infarctions, direct iatrogenic vascular injury leading to iatrogenic surgery related stroke, pseudo aneurysms and vascular thrombosis including arterial, venous or dural venous sinuses. Each one of these subunits of ischemic cerebrovascular complications share commonality by posing a severe detrimental consequence to the life of the patient, but these all subunit complications have variability in its occurrences and different diagnostic and therapeutic required. [1]

There are a number of causes for the development of cerebral vasospasm. Accordingly, spontaneous & traumatic subarachnoid hemorrhage from ruptured cerebral aneurysms & traumatic brain injury respectively, post cranial tumor resections along with cerebral inflammations from infectious process (bacterial meningitis, cerebral malaria & neurocysticercosis) are responsible for the majority of cerebral vasospasms (2-13). In addition, though not common, cerebral vasospasms are reported to occur following arachinoid cyst fenestration (14), intracerebral hematoma (ICH) alone (15), spontaneous rupture of dermoid cysts (16) & evacuation of acute subdural hematoma (17). Rarely, cerebral vasospasms can also occur in the absence of identifiable intracranial etiology as evidenced by a case study that showed its occurrence in a patient who had only spontaneous acute spinal subdural hematoma (18).

The incidence of cerebral vasospasm is highly variable based on the specific causes of cerebral vasospasm. The chance of getting cerebral vasospasm following subarachnoid hemorrhage of spontaneous aneurysmal rupture is very high compared to vasospasm following brain tumor resection. According to a prospective study done for 38 patients with ruptured aneurysmal subarachnoid hemorrhage, 36.8% of the patients developed cerebral vasospasm; the mean time for its development being 8.4 ± 2.8 days if Trans Cranial Doppler (TCD) &/ EEG was done while its diagnosis with delayed cerebral ischemia clinical signs delays by 12.5 ± 5.3 h. (2)

The incidence of cerebral vasospasm following tumor resection was rare (only 1.9 %) according to systematic review on 470 skull base tumor surgeries performed. [9] ‘Cerebral vasospasm’ after tumor resection is a rare but challenging complication with very high morbidity and mortality in

reported cases. Vasospasm following brain tumor surgery shares some of the same clinical variables (time interval, causative factors, morbidity and death rates) of vasospasm after aneurysmal subarachnoid hemorrhage. A high index of suspicion is required for early diagnosis and prompt management which are key elements of final outcome. [13]

According to a systemic review of 40 patients who developed cerebral vasospasm following brain tumor resection, Pituitary tumors and meningiomas were the most common pathologies (42.5% and 17.5%, respectively) that are associated with vasospasm. Craniopharyngioma, vestibular shwanoma and epidermoid cyst were tumors which gave vasospasm to 2 (5%) patients each. Similarly, astrocytoma, Colloid cyst, Dermoid cyst, Ependymoma, Esthesioneuroblastoma, Adenocarcinoma & Hemangioma contributed to 1 (2.5%) of patients each among the 40 cases of cerebral vasospasms that developed following tumor resection. [13]

Similarly, according to a prospective study conducted in 22 patients to see the changes of intracranial cerebral blood flow velocities (CBFV) with bacterial meningitis using TCD, 18/22 had high CBFV with marked CBFV (>210 cm/sec) occurring in 7 of patients and correlated with poor outcome. (12)

Pathophysiology /mechanisms/ for the development of cerebral vasospasm

Why does cerebral vasospasm of any cause and its sequelae (DCI) occur?

Despite the exact mechanism of why cerebral vasospasm is not fully understood, it is known that the end mechanism is more or less similar even if the initiating events are somewhat different. There are numerous mediators for the occurrence of ischemic cerebral complications including cerebral vasospasm following any cause. But, the effect of direct vessel manipulations, transient global ischemia, blood & its products and inflammation are the most important inciting agents for

the occurrence of vascular dysfunction and its sequel, cerebral vasospasm as will be detailed below [19-53].

I). Effect through direct manipulation of cerebral vessels during cranial neurosurgery

Direct manipulation of vessels can allow calcium influx via stretch-activated channels and subsequent vessel smooth muscle contraction and vasospasm occurs as the influxed calcium binds CaM and activaes MLCK into its active form. The activated MLCK phosphorylates the MLC to MLCp and causes vasoconstriction and vasospam. [20]

II). Effect through transient global ischemia & Diffuse Cerebral edema

The first physiologic insult after SAH of any cause is a transient global ischemia as intracranial pressure approaches mean arterial pressure. [21-22]This ischemic episode can trigger vascular dysfunction even before the toxic effects of hemoglobin are realized.First, the process is initiated through an induction of the sympathetic nervous system, [23]often referred to as the "sympathetic surge" or "catecholamine surge". Initial activation involves both ischemic injury to the hypothalamus [24] as well as compression of the brain stem. [25]

Separate from sympathetic nervous system activation, transient global ischemia causes endothelial injury and BBB disruption as well. Endothelial injury and even apoptotic cell death have been reported to occur within the first 24 hours post-SAH, [26-27]which disrupts the BBB and promotes coagulation by exposing subendothelial collagen. [28] Acute global ischemia also has consequence in stimulation of the endothelin-1 pathway.

III). Effect through blood and its products

Currently, there is little doubt on the vaso-spasmogenic effect of blood and its products either directly or indirectly. But, it is proved almost impossible to identify a single causative agent responsible for cerebral vasospasm among various vasoactive substances. The lack of cure for CVS that addresses ferrous hemoglobins necessitates that other possibilities also be considered. What is clear, however, is that prolonged exposure of cerebral arteries to perivascular blood is necessary for the development of cerebral vasospasm. [19-20, 29]Accordingly, a considerable body of evidence suggests that oxyhemoglobin (OxyHb; ferrous hemoglobin) is the primary

spasmogenic agent responsible for the development of cerebral vasospasm (CVS) [29-30]. Oxyhemoglobin (OxyHb) is present in high concentrations in the cerebrospinal fluid (CSF) during the time of CVS. Oxyhemoglobin and deoxyhemoglobin concentrations in the CSF peak around day 7 post-SAH in primates, [31-32] roughly corresponding to the onset of secondary brain injury. Hence, erythrocytes have been shown to be the component of blood necessary for vasospasm to develop, and the most vasoactive substance within them is OxyHb [33] Moreover; changes in OxyHb concentration within the subarachnoid space tend to mirror the evolution of CVS [29]. The vasospasmogenic effect of oxyhemoglobin is multifaceted although OxyHb may be responsible for the initiation of vasospasm (see below). ***What do blood & its products (e.g. OxyHb) do?*** There are detailed mechanisms for why an actual vasospasm & subsequent cerebral infarction occurs.

Blood products have direct vascular vaso-constrictive effect. This is mediated through Ca2+-dependent and ca2+ independent vasoconstriction. How? The blood products released after SAH probably stimulate cell membrane receptors (G-protein-coupled receptors and receptor tyrosine kinases) for Ca2+-dependent vasoconstriction [34-35] while the activation of rho kinase, which follows the activation of small G-protein rhoA, inhibits the dephosphorylation of MLC by myosin light chain phosphatase (MLCP) in the case of Ca2+-independent vasoconstriction [36]; thus contributing to the development of CVS.

Hemoglobin also stimulates the production of endothelins (most potent vaso-constrictive agent); the imbalance of nitric oxide (most potent vasodilator) and endothelin could be an important cause of pathological arterial contraction.

Oxyhemoglobin is also a potent scavenger of NO and reduces the availability of NO in the surrounding cerebral vasculature. [37-38]Production of NO is unable to compensate for this loss owing to a rise in asymmetric dimethylarginine, [39-40]an endogenous nitric oxide synthase (NOS) inhibitor, and decreased expression of endothelial- and neuronal-specific NOS isoforms.[41-42]The remaining NOS enzymes are also damaged through oxidation of essential enzymatic cofactors by reactive oxygen species from hemoglobin metabolism and local inflammation. This results in the "NOS uncoupling" phenomenon whereby consumption of substrates L-arginine and O2 is "uncoupled" from NO production and instead results in superoxide (O2· -) generation.[43] The presence of superoxide further

reduces NO bioavailability by reacting with the remaining NO to form peroxynitrite, a potent oxidizing agent. [44]This perfect storm of vasoconstrictive, NO-depleting, and reactive oxygen species-generating events after SAH is central to the resulting vascular dysfunction.

Oxyhemoglobin that penetrates into the brain parenchyma via the paravascular and glymphatic systems suppresses NO/cyclic guanosine monophosphate (cGMP) signaling and causes phenotypic conversion of pericytes to a hypercontractile form, leading to a reduction in capillary diameter [45]. Pericytes (mural cells of blood micro vessels) play an important role in the control of capillary diameter and brain blood flow. Oxyhemoglobin also induces pericyte constriction by increasing the production of reactive oxygen species (ROS) and endothelin-1 in astrocytes [45]. Global ischemia caused by elevated intracranial pressure after subarachnoid hemorrhage also constricts pericytes, leading to a reduction in capillary diameter and blood flow in the microcirculation [46].

IV) Effect through inflammatory mediators released following subarachnoid hemorrhage /infectious or inflammatory process/ tumor resetion/

Systemic inflammation has a role in the occurrence of cerebral vasospasm regardless of the cause, be infectious, traumatic, aneurysmal etc. Besides with the direct effect of cytokines, vasculitis is found to be an important cause of cerebral vasospasm be in the case of infectious process (e.g. TB meningitis) or SAH of any cause as evidenced by proliferative changes with intimal thickening with resultant stenosis or occlusion, and necrotizing vascular lesions. The vasculitis & vasospasm tends to be most prominent in vessels passing through the basilar exudate. [47-49]

A mediator, which was found to be of key importance in reduction of the risk of cerebral vasospasm in bacterial meningitis, cerebral malaria, brain injury, and subarachnoid haemorrhage, is nitric oxide (NO), but its release (from direct cytokines effect, e.g TNF) or availability (scavenged by free radicals) will be low. Hence, the cytokines (mediators of inflammation) exert their cerebral vasospasmin effect directly/indirectly/. [44, 50-53]

Risk factors for incidence & severity of the cerebral vasospasm

The risk of infarction depends on adequacy of collateral blood supply, cardiac output, blood pressure, and intracranial pressure.

Risk factors for cerebral vasospasm following tumor resection

Table 1. Risk factors for tumor resection related cerebral vasospasm

1.1. Preoperative risk factors		Suggested explanations	Reference
Location	Sellar & suprasellar extension	• Because of anatomic proximity with circle of Willis	[9,54-61]
Cranial fossa	Middle> Anterior >Posterior	• common location for meningioma • proximity with circle of Willis • proximity with cisterns • more surgical manipulation • Vasospasm in posterior fossa surgery is rare but tends to be diffuse if it occurs.	[9,54-61]
Tumor type	Meningioma	• Tend to encase vessels • Can parasitize branches of ICA • Intraoperative bleeding and facilitate spillage of blood in the subarachnoid space. • more surgical manipulation	[54,56,59,62-63]
	Pituitary	• anatomic proximity with circle of Willis • Middle cranial fossa location	[60-61, 64-65]
	Craniopharyngioma & dermoid cyst	• release lipid metabolites • Alter intracellular calcium levels with certain growth factors. • Cerebral vasospasm was seen on the side of surgery. It was never seen	[66-69]

	when the lamina terminalis approach was used, and was seen following resection through carotico-optic and interoptic corridor. ($p<0.05$).	
High grade glioma	According to a **retrospective a cohort of 239 patients who underwent surgical resection of HGG between 2013 and 201,** infarcts were more common in patients undergoing surgery for tumors located in the insula (23%) and temporal lobe (57%), p = 0.019 and p = 0.01, respectively. In addition, after a multivariate analysis, surgery for insular HGG had the strongest association with postoperative infarcts (multivariate analysis: odds ratio [OR] 2.41, 95% confidence interval, [CI] 1.02–7.73, p = 0.045, followed by temporal lesions (OR 2.81, 95% confidence interval, [CI] 1.07–5.39, p = 0.033). Most (16/30; 53%) of the strokes involved segments of the middle cerebral artery (MCA) territory, of which 7/16 (44%) were insular and involved small perforating arteries.	[70]
Vessel Encasement	More manipulation + bleeding	[54-61,64]
1.2. Intraoperative risk factors	Suggested explanations	References
Manipulation	See above +pathogenesis	[54-61, 64]
Content spillage		[66-69]
Use of only saline instead of additional surgical site papavarine /nimodipine/	Significant decrease in caliber of MCA shown the normal saline group ($P < 0.05$) but not in the nimodipine group.	[62]

Craniotomy vs Trans-sphenoidal approach	It seems that technique and complication avoidance that matters most and vasospasm is known to occur in both procedures though large study comparing the two is lacking.	[9,13,61, 64-65]
1.3. Postoperative risk factors	Suggested explanations	References
Tumor bed ICH	Likely from the blood and its byproducts 'effect on cerebral vessels	[29,54-61,64]
CT grade of SAH/	A slower rate of subarachnoid clot clearance has also been shown to be an independent predictor of vasospasm, although this is not an easy measurement in clinical practice.	[71-75]
Cerebral salt wasting (CSW)+ DI + hypovolemia	Probably from the hypovolemia's effect on cerebral vessels and hpo & hypernatremia effect on brain	[76-77]
Hypothalamic dysfunction	Likely from altered cerebral auto-regulation	[62,78]
Meningitis & /inflammation/	Likely from the release of inflammatory mediators and their effect on cerebral vessels	[47-48]

Diagnostic workups for iatrogenic ischemic stroke (direct vessel injury), cerebral vasospasm, EBI & DCI

While the diagnosis of patients with post-surgery/iatrogenic/ ischemic stroke is pretty simple and diagnosed with plain CT/MRI, the diagnosis of cerebral vasospasm & delayed cerebral ischemia is a bit complicated and needs better experience.

Patients asymptomatic before screening have low rates of CVS and seem to be at negligible risk of developing DCI. Routine screening of asymptomatic patients seems to have little utility. Screening may still be considered in patients with possible symptoms of DCI or those with examinations too poor to clinically detect symptoms because finding CVS may be useful for risk stratification and guiding management. [79]

There are 2 main approaches to imaging VS: imaging arterial luminal narrowing (angiographic VS) and imaging microvascular dysfunction of the brain parenchyma (DCI). Although angiographic VS has historically been the focus of imaging, evaluating DCI has increasingly gained importance because it has been shown to be more closely associated with clinical outcomes. [79]

Digital Subtraction Angiography (DSA)

DSA is considered the reference standard for detection and monitoring of angiographic VS. It also allows simultaneous treatment. (274).

CT angiography (CTA)

CTA is a minimally invasive and less expensive alternative for angiography. A meta-analysis summarizing multiple CTA based studies showed approximately 80% sensitivity and 93% specificity overall, with a sub-analysis indicating better diagnostic performance for proximal segmental VS.[80-81] A recently published systematic review with intra-observer and inter-observer analysis reassessing the utility of CTA in VS found 14 diagnostic accuracy studies and concluded there was a paucity of data and heterogeneity of methods.[82] The intra-observer and inter-observer analysis component of the same study evaluated 50 patients with ASAH in a multiple-reader study and found inter-rater reliability to be at best moderate. Thus, the investigators concluded that the diagnosis of VS with CTA alone did not show sufficient repeatability to support its widespread use as a stand-alone modality to guide clinical

management.[82]The discrepancy with earlier diagnostic accuracy studies may stem from differences in the studied patient population as well as the evolution of CTA application in ASAH over time. In the earlier studies, CTA as a noninvasive way to monitor VS was compared directly with DSA, thus focusing on patients with more severe disease and worse outcomes; subsequently, the less invasive test (CTA) shifts to a population of patients with less severe disease who may not undergo DSA and are instead followed clinically and with TCD/follow-up CTA, precluding direct comparison.[82]

MRI

MR-based imaging is well established for the evaluation of acute infarction using diffusion-weighted imaging (DWI). Recent advances in MR-based vascular imaging, particularly vessel wall imaging (VWI), as well as perfusion imaging with ASL and dynamic contrast-enhanced (DCE) techniques, have challenged this view. VWI showed correlation between vessel wall enhancement and DCI/poor clinical outcomes.[83]

Trans-cranial Doppler (TCD)

Vasospasm causes an increase in blood flow velocity, which can be measured by transcranial doppler (TCD). Normal MCA blood flow velocity is <120 cm/s, velocity ranging from 120 to 200 cm/s indicates mild vasospasm, and velocity >200 cm/s is taken as severe vasospasm. Also, an increase by 50 cm/s in 24 h indicates presence of vasospasm. However, it is important to differentiate between vasospasm and hyperemia (generalized raised flow velocity). These two can be differentiated by Lindegaard index, which is a ratio of flow velocities in ipsilateral MCA to extracranial ICA. Lindegaard ratio <3 denotes hyperdynamic circulation, 3–6 indicates mild-moderate vasospasm and >6 denotes severe vasospasm. [84-85]Low pulsatility index is an independent predictor of symptomatic large vessel vasospasm. [85] Angiographic vasospasm (VS) can be monitored with transcranial Doppler ultrasonography; however, computed tomography angiography has a higher diagnostic accuracy when using digital subtraction angiography as the reference standard. [79]

The role of TCD as a noninvasive screening tool at the bedside is not a mandated standard of care in aSAH due to the paucity of evidence on clinically relevant outcomes despite recommendation by national guidelines. [86]currently, the American Heart Association's evidence-based national guidelines recommends the use of TCD for the management of SAH indicate the use of transcranial

Doppler ultrasonography to be a reasonable tool for vasospasm monitoring. [87] *For the ACA and PCA, diagnostic thresholds for VS are 80 cm/s and 85 cm/s, respectively. [88]*

Techniques of Transcranial Doppler Ultrasound

The transtemporal window consists of an anterior, middle, and posterior window. However, in practice, there is usually only one useful window. Using this window, the intracranial carotid artery (ICA) bifurcation can be identified at depths of 55 to 65 mm with simultaneous flow toward and away from the probe as the ICA bifurcation terminates in the anterior (flow away from the probe) and middle (flow toward the probe) cerebral arteries (ACA and MCA). The ICA terminus is a convenient anatomic landmark to locate the vessels of the anterior circulation. The MCA, viewed at depths of 35 to 55 mm, runs laterally and slightly anterior after its origin from the ICA. Flow in the MCA should be toward the probe until the MCA trifurcation where flow becomes bidirectional. The ACA, which can be viewed at depths of 60 to 70 mm, begins coursing medially and then anteriorly after the ICA bifurcation. The ACA flow should be away from the probe. The posterior cerebral artery (PCA) can also be insonated through the transtemporal window. In general, the PCA is found 1 to 2 cm posterior to the ICA bifurcation, but in the same plane as the circle of Willis. The PCA can be found posterior and deep to the ICA and MCA, at a depth of 60 to 70 mm. Flow in the proximal PCA (P1 segment) is toward the probe and in the distal PCA (P2 segment) away from the probe. The PCA will always exhibit lower velocities than the MCA. It is important to note that in individuals where the PCA derives most of its flow from the ICA through a large posterior communicating artery (Pcom), the so-called fetal PCA configuration, the P1 segment is hypoplastic and may be very difficult to identify.1

The transorbital window can be used to examine the carotid siphon and the ophthalmic artery. The probe is placed over the closed eyelid and the beam power is kept under 10% of maximum power in order to minimize the risk of traumatic subluxation of the crystalline lens of the eye. In addition to the amount of energy, the total time of insonation also needs to be considered and kept to a minimum to avoid further soft tissue damage. The probe is directed toward the optic canal at a depth of 55 to 70 mm to insonate the carotid siphon. Flow direction can be used to identify the different segments of the siphon. In general, flow is toward the probe in the infraclinoid siphon, flow in the genu is bidirectional, and flow is away from the probe in the supraclinoid segment of

the siphon. The ophthalmic artery can be found at depths of 40 to 50 mm. Flow in the ophthalmic artery should be toward the probe.

The suboccipital window with the neck flexed, can be used to insonate the basilar and vertebral arteries. The basilar artery is typically found at depths of 60 to 70 mm and can sometimes be followed to depths up to 100 mm. Although the basilar artery is found with probe directed medially, vertebral arteries are best insonated with the probe slightly shifted laterally, at a depth of 80 to 115 mm. Flow at the top of the basilar and in the vertebral arteries is typically away from the probe.

The submandibular window is at the angle of jaw and can be used to locate the distal ICA in the neck at a depth of 40 to 60 mm. Flow at this point is usually away from the probe.

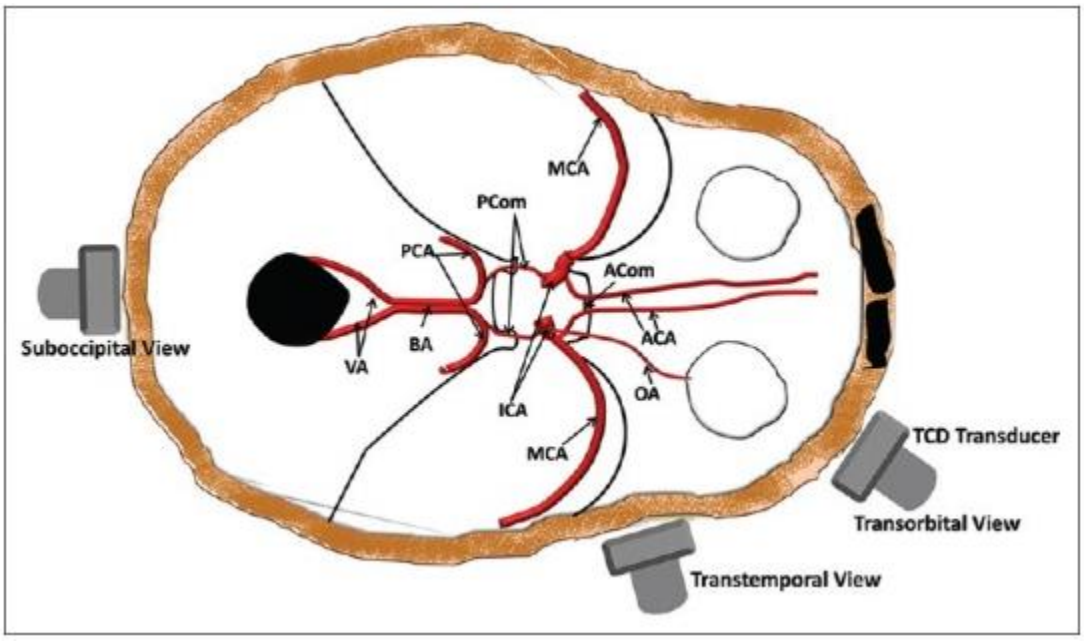

Figure. Acoustic windows for insonation of different cerebral arteries [85]

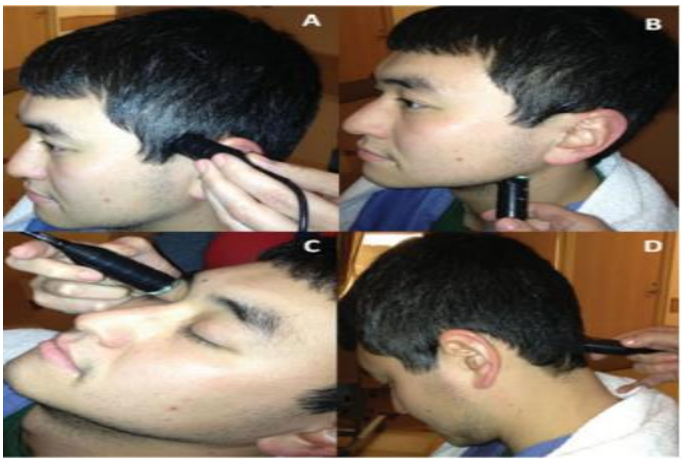

Figure Four acoustic windows commonly used in transcranial Doppler examination: transtemporal window (A), submandibular window (B), transorbital window (C), suboccipital window (D).[85]

Reliability of TCD in prediction of cerebral vasospasm

Low or very high MCA flow velocities (<120 or >200 cm/s) reliably predict the absence or presence of clinically significant vasospasm. Intermediate velocities between 120 and 199 cm/s are unreliable and inconclusive for the determination of significant angiographic vasospasm. Routine daily measurement of TCD velocities in SAH patients should be advocated till the expected period of vasospasm. Diagnostic accuracy of TCD for detection of ACA and PCA vasospasm is limited. The use of TCD for detection of posterior circulation vasospasm that comprises BA and VA vasospasm appears promising. However, further data are required to recommend the routine use of TCD for posterior circulation stroke.[85]

Once vasospasm after tumor resection occurs and patients became symptomatic, morbidity and death rates are high. Almost half of patients did not recover from their major neurological deficits and the death rate was 30%. Given the high morbidity and mortality associated with this complication once patients become symptomatic, identification of predisposing factors is key for a prompt diagnosis & treatment as there are high efficacy hyperdynamic therapy and endovascular pharmacological and mechanical angioplasty in counteracting the clinical effects of vasospasm. [13] Accordingly, the treatment of cerebral vasospasm & DCI basically involves the use of oral nimodipne, hemodynamic augmentation and endovascular interventions as detailed below.

Nimodipine administration (Class I, Level of Evidence A) [89-90] is the only evidence-based pharmacologic therapy for improving outcomes following vasospasm [91]. It does not treat the vasospasm but improves the neurological outcomes by limiting DCI. A Cochrane review showed that calcium channel blockers reduced the risk of poor outcome: the relative risk (RR) was 0.81 [95% confidence interval (CI), 0.72–0.92] with a number needed to treat of 19 (95% CI, 1–51). However, subgroup analyses for poor outcome according to the type of calcium channel blockers and route of administration showed a significant result only for oral nimodipine treatment. These findings indicate that oral nimodipine treatment improves the overall outcome [92].

Hemodynamic management of cerebral vasospasm

Currently, hemodynamic augmentation by achieving euvolemia & induced hypertension **for patients with DCI** with the intention of improving cerebral blood flow (CBF) to optimize the cerebral perfusion pressure is preferred over the Triple-H therapy (hypervolemia, hypertension, and hemodilution), which was considered for many decades to increase cerebral blood flow in patients with aneurysmal SAH and to prevent and treat cerebral vasospasm. **The goal in hypertension induction is to increase mean arterial pressure (MAP) by 20% or target a MAP at 100-110 mmHg**. Efforts to reach the target blood pressure in patients with congestive heart failure, myocardial ischemia, and other cardiac comorbidities may be limited to avoid other serious complications that might develop from cardiac decompensation. In patients with signs of vasospasm and an unsecured aneurysm, blood pressure elevation should be cautious**. The**

preferred vasopressors to induce hypertension are norepinephrine, phenylephrine, and possibly dopamine. [89-90]

Endovascular intervention for cerebral vasospasm

When medical options have been exhausted, or patient comorbidities prevent full application, endovascular treatment (**Cerebral angioplasty and/or selective intra-arterial vasodilator therapy) is reasonable in patients with symptomatic cerebral vasospasm, particularly those who are not rapidly responding to hypertensive therapy** (*Class IIa; Level of Evidence B*).[90] In other word, when the first line therapy for new onset DCI & cerebral vasospasm fails, rescue therapeutic approch is indicated (see figure below) [93]. The primary goal of endovascular treatment is to prevent cerebral infarction by increasing blood flow to territories that have been compromised by vasospasm. [94]

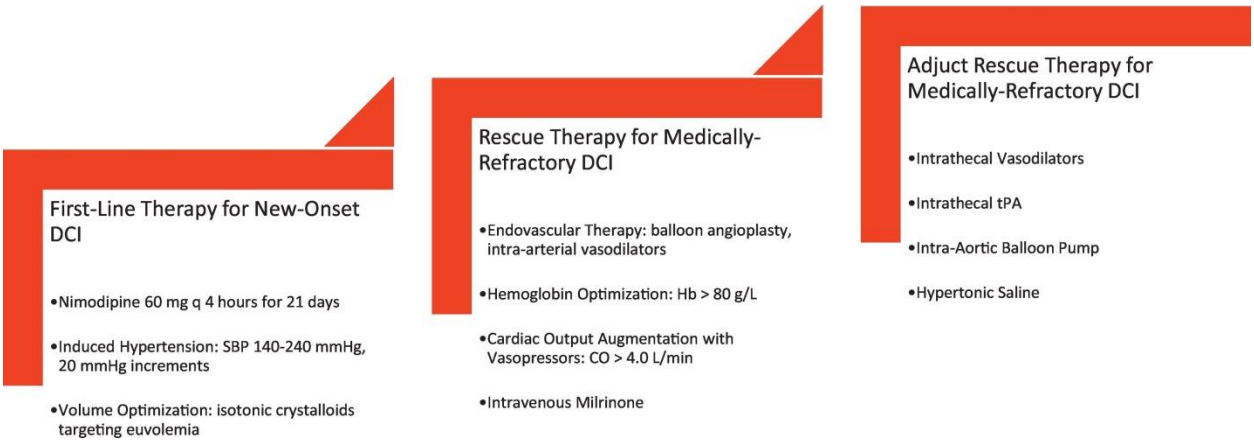

Figure Tiered approach to the management of delayed cerebral ischemia [93]

Outcome after endovascular therapy for cerebral vasospasm?

Although angiographic outcomes are favorable in nearly 70% of patients, endovascular therapy has not consistently demonstrated superiority to traditional medical treatment in improving clinical outcomes, and there is a risk of procedure-related ischemic complications after endovascular vasospasm therapy. [95] According to a series of eight patients with symptomatic vasospasm following tumor resection treated with 6 patients underwent intraluminal angioplasty Angiographic results were good in all patients. Significant clinical improvement wasseen in six of the eight symptomatic cases. [13]

1.4. Conceptual framework

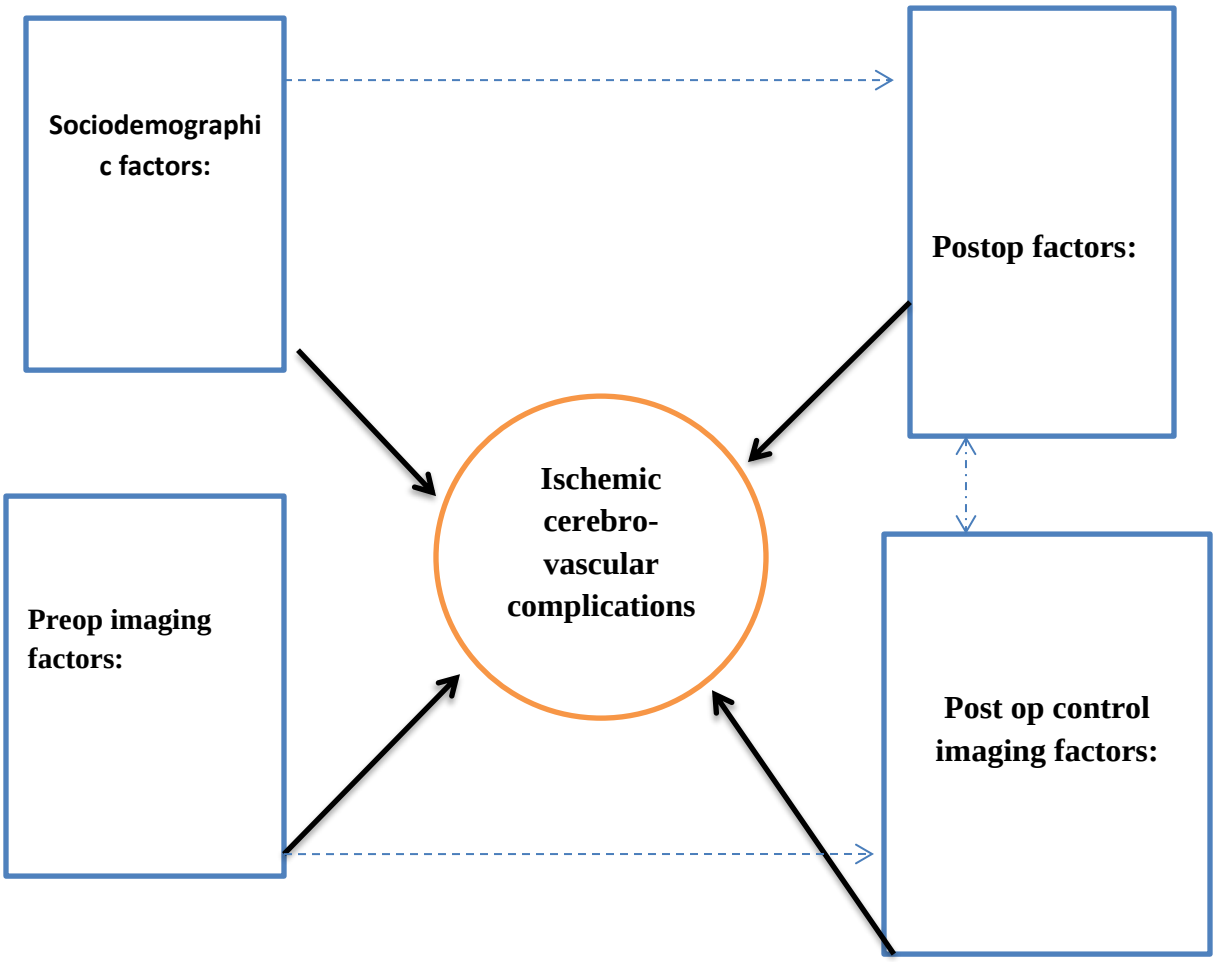

Figure1: Conceptual frame work showing the relation between the outcome and different factors

1.5.Significance of study

Cerebral ischemic complications in brain surgery are extremely severe complications that the attending neurosurgeon and neuro-critical care team must always be vigilant to have optimal patient care and outcome. For this to be the case, it is reasonable to know how prevalent it is, what predisposing factors cause it, how precisely it is diagnosed, what degree of unfavorable outcome it carries, what important lifesaving therapeutic options are administered and the potential prevention strategies used. In addition, knowing the experience of the setup that one operates at is extremely important in dealing with the diagnosis, treatment, prevention and improving the outcome of patients with this costly complication. Furthermore, prognostication of patients after surgery is of great importance for early intervention to be made. Building a cerebro vascular complication risk prediction model can be used to classify patients as at higher and lower risk risk of the outcome. This can be made right after undergoing surgery using early obtainable prognostic determinants. Hence, this study will be of paramount in that it will provide baseline incidence of cerebral ischemic complications in our setup.

- Help identify the modifiable predisposing factors for ischemic cerebral complications in our setting.
- Assess the practical diagnostic challenge to detect each one of the cerebral ischemic complications in general and cerebral vasospasm in particular.
- Highlight the available therapeutic options available to help treat each one of the spectrums of ischemic cerebral complications to those in need in our setting.
- Help detect the patterns of ischemic cerebral complications in patients with brain tumor undergoing surgery for it in our setting.
- Provide baseline outcome and prognosticator data which is based on the experience of our setting.
- Help outline some preventive strategies based on existing uptodate evidences and by our study finding.
- Contribute new knowledge to scientific literature and scientific community based on a study done in our setting; a low income setting.
- Improve the standard of care of patients.

2. Objectives

2.1. General objective

- To assess the incidence and predictors of surgery related cerebro-vascular ischemic complications among patients undergoing brain tumor resection at BLH & MCM from April 1-September 30; for 6 months

2.2. Specific objective

- To assess the incidence of cerebral vascular ischemic complications in the study period & area.
- To identify predictors of cerebral vascular ischemic complications in the study period & area
- To identify the major diagnostic and therapeutic challenges to patients with cerebral vascular ischemic complications in the study period & area
- To Develop a risk prediction model for the prediction of cerebral vascular ischemic complications among the study subjects

3. Methodology

3.1 Study design and period

A hospital based prospective observational cohort follow-up study will be conducted for the occurrence of ischemic cerebral vascular complications among patients who underwent cranial surgery for brain tumor resection. The study will be conducted starting from April 1-September 30; for 6 months.

3.2 Study setting

The study will be conducted at two of teaching hospitals of Addis Ababa University: BLH & MCM.

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3.3 Source Population

All patients undergoing brain tumors surgery in two of Addis Ababa University affiliate teaching hospitals: Black Lion Hospital (BLH) and Mysung chrstian Medical Hospital (MCM).

3.4 Study Population

All patients undergoing brain tumors surgery two of Addis Ababa University affiliates teaching hospitals: Black Lion Hospital (BLH) and Mysung chrstian Medical Hospital (MCM) and fulfilling the inclusion criteria with in the study period.

3.5 Inclusion and Exclusion criteria

Inclusion criteria:

All patients who get routine appropriate follow-up post op diagnostic imaging and specific need based diagnostic imaging after undergoing cranial tumor resection for brain tumor will be included in the study.

Exclusion criteria: Patients who refused consent will be omitted in the study.

Patients with no appropriate follow-up and need based diagnostic imaging will be excluded from the study.

3.6 Sample size determination [62]

Compare proportion with a dichotomous outcome between two samples, using the Chi-squared statistic (or z test).

Your study includes Group 1 (exposed or active treatment) and Group 0 (unexposed or control treatment). You know P0 (outcome proportion in unexposed or control group) and either P1 (outcome proportion in exposed or active treatment group), RR (risk ratio), or OR (odds ratio).

If you don't know P0 but do know P (the prevalence of the outcome in the population) and Q1 (the proportion of exposed individuals in the population), and you can estimate RR, use this alternative calculator. Note the distinction between Q1 (proportion of exposed individuals in the population) and q1 (proportion of exposed subjects in your study).

α (two-tailed) Threshold probability for rejecting the null hypothesis. Type I error rate.=0.05

β (Probability of failing to reject the null hypothesis under the alternative hypothesis. Type II error rate) =0.2

q1 (Proportion of subjects that are in Group 1 (exposed))=0.5

q0 (Proportion of subjects that are in Group 0 (unexposed); 1-q1)=0.5

P0 (Risk in Group 0 (baseline risk)=0.4

(Reference used:https://pubmed.ncbi.nlm.nih.gov/34343357/)

The standard normal deviate for $\alpha = Z\alpha = 1.9600$

The standard normal deviate for $\beta = Z\beta = 0.8416$

Pooled proportion = P = (q1*P1) + (q0*P0) = 0.3350

$A = Z\alpha\sqrt{P(1-P)(1/q1 + 1/q0)} = 1.8502$

$B = Z\beta\sqrt{P1(1-P1)(1/q1) + P0(1-P0)(1/q0)} = 0.7869$

C = (P1-P0)2 = 0.0169

Total group size = N = (A+B)2/C = 411

Continuity correction (added to N for Group 0) = CC = 1/(q1 * |P1-P0|) = 15

Sample size (with continuity correction)

	N	Outcome+	Outcome-
Group 1:	221	60	161
Group 0:	221	88	133
Total:	442	148	294

Sample size (without continuity correction)

	N	Outcome+	Outcome-

Group 1:	206	56	150
Group 0:	206	82	124
Total:	412	138	274

Note: This calculator uses the normal distribution (with and without the continuity correction) as an approximation to the binomial distribution.

3.7 Sampling procedures

All eligible subjects will be included in the study.

3.8 Variables of the study

3.8.1. Outcome variable and ascertainment

The outcome variable is vascular ischemic cerebral complications (Yes/No). It includes angiographic cerebral vasospasm, clinical cerebral vasospasms or delayed cerebral ischemia /DCI/, DCI related cerebral infarction, ischemic stroke, cerebral venous or arterial thrombosis & pseudo aneurysms.

This outcome will be assessed in patients who underwent brain tumor surgery at the immediate postop, 3-4th post op day, 7-8th post op day, 12-14th post op day and 30th postop day. In addition, the patient will be followed and worked up for the occurrence of this complication each time the patient deteriorates and has clinical conditions suggestive of the occurrence of these complications. These follow up periods are selected because most ischemic vascular ischemic complications do occur in this time periods as per existing evidences and after having a 30 days of follow up, one can provide short term surgical outcomes of the studied population. As ischemic cerebral vascular complication encompasses, a spectrum of ischemic vascular complications, different clinical and diagnostic investigations will be used as will be detailed below.

Accordingly, the direct iatrogenic vascular injuries will be detected by the control CT/MRI/ obtained on the immediate postop scans as this is a routine practice. Similarly, angiographic cerebral vasospasms will be diagnosed with transcranial Doppler ultrasound in the time frames outlined above in collaboration with radiology department & neuro-critical care anesthesiology

team. On the contrary, clinical vasospasm, aka, delayed cerebral ischemia (DCI) will be diagnosed by a set of criteria set by the international expert panel for SAH research 2010. Accordingly, DCI is diagnosed when there is the occurrence of new focal neurological impairment *lasting for at least 1 hour* (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect), or a decrease of at least 2 points on the Glasgow Coma Scale, which is not apparent immediately after aneurysm occlusion/tumor excision/ and cannot be attributed to other causes. This requires ruling out other causes of neurological deterioration like HCP, re-bleeding, electrolyte disorders, seizures, and hypoxia before making diagnosis of vasospasm and the symptoms must be new; should not present in the first 48 hours of the surgery. Similarly, DCI-related cerebral infarction was defined as follows according to international expert panel for SAH research 2010: diagnosis of cerebral infarction performed by either a brain CT or MR scan within 6 weeks after SAH, or on the latest CT or MRI scan made before death within 6 weeks, or proven at autopsy, not present on the CT or MRI scan between 24 and 48 h after early tumor resection/aneurysm occlusion, and not attributable to other causes, such as direct vessel injury during tumor resection/surgical clipping or endovascular treatment.

Post tumor excision ischemic stroke will be diagnosed by the imaging evidence of cerebral infarction that resulted from either direct vascular injury during tumor excision, embolic accidents elsewhere in the body, vessel thrombosis or delayed cerebral vasospasm related cerebral infarctions of any infarct volume.

Cerebral vessel thrombosis (arterial, veins and venous sinus) will be diagnosed when CTA/MRA & MRV confirmed the presence of thrombus to vessel suspected.

Pseudo aneurysm will also be diagnosed by CT angiography.

Once the diagnosis of cerebral ischemic complication is made, the patients clinical course, treatments provided and the outcome will be followed for 30 days and will be compared with those patients who do not developed ischemic cerebral complications after undergoing brain tumor surgery.

3.8.2. Predictors/prognostic determinants

A. Sociodemographic factors

- Preop comorbid factors
- Smoking
- Preop karnofsky performance status (KPS)

B. Preop imaging factors

- Tumor type
- Location
- Size
- Preop radiation/emboliation
- Vessel encasement
- Intraop surgical factors
- Surgical approach
- Extent of resection
- Intraop brain edema
- Intraop brain contusion
- Vessel manipulation
- Iatrogenic vessel injury
- Experience of surgeon in years of service provided
- EBL
- Use of hemostatic agents
- Difficulty of securing hemostasis
- Intraop/preop/ use of nimodipine

C. Postop factors

- Postop clinical status & course

D. Post op control imaging factors

- Extent of resection
- Tumor bed hematomas (SaH, EDH,SDH,IVH,), HCP, pneumocephalus, contusion, brain edema, cerebral infarction, etc)

- Hypernatremia/hyponatremia
- Trans cranial Doppler ultrasound (TCD) findings

3.9. Operational definitions

Delayed cerebral ischemia (DCI) is new focal neurologic deficit to suggest delayed cerebral ischemia (DCI), as defined by the occurrence of focal neurological impairment lasting for at least 1 hour (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect), or a decrease of at least 2 points on the Glasgow Coma Scale, which is not apparent immediately after tumor resection, and cannot be attributed to other causes OR those with examinations too poor to clinically detect symptoms.

DCI-related cerebral infarction was defined as follows according to international expert panel for SAH research 2010: diagnosis of cerebral infarction performed by either a brain CT or MR scan within 6 weeks after SAH, or on the latest CT or MRI scan made before death within 6 weeks, or proven at autopsy, not present on the CT or MRI scan between 24 and 48 h after early tumor resection/aneurysm occlusion, and not attributable to other causes, such as direct vessel injury during tumor resection/surgical clipping or endovascular treatment.

Post tumor excision ischemic stroke will be diagnosed by the imaging evidence of cerebral infarction that resulted from either direct vascular injury during tumor excision, embolic accidents elsewhere in the body, vessel thrombosis or delayed cerebral vasospasm related cerebral infarctions of any infarct volume.

Cerebral vessel thrombosis (arterial, veins and venous sinus) will be diagnosed when CTA/MRA & MRV confirmed the presence of thrombus to vessel suspected.

Pseudo aneurysm will also be diagnosed by CT angiography.

Angiographic vasospasm defined as moderate-to-severe arterial narrowing on digital subtraction angiography not attributable to atherosclerosis, catheter-induced spasm, or vessel hypoplasia. About 70% of patients may have angiographic narrowing but clinically may not be evident in all.

Clinical vasospasm defined as neurological deterioration deemed secondary to vasospasm after other causes are eliminated. It is seen in 20–40% of patients. There may be alteration in consciousness, disorientation, and occurrence of new focal neurological deficit corresponding to the artery involved, usually around 3–14days after SAH. We should rule out other causes of neurological deterioration like HCP, re-bleeding, electrolyte disorders, seizures, and hypoxia before making diagnosis of vasospasm (273).

Trans-cranial Doppler (TCD)

Vasospasm causes an increase in blood flow velocity, which can be measured by transcranial doppler (TCD). Normal MCA blood flow velocity is <120 cm/s, velocity ranging from 120 to 200 cm/s indicates mild vasospasm, and velocity >200 cm/s is taken as severe vasospasm. Also, an increase by 50 cm/s in 24 h indicates presence of vasospasm.

Lindegaard index is a ratio of flow velocities in ipsilateral MCA to extracranial ICA.

Lindegaard ratio <3 denotes hyperdynamic circulation, 3–6 indicates mild-moderate vasospasm and >6 denotes severe vasospasm.

Modified Fisher grading scale (0-4) is the most important risk factor predictive of vasospasm after SAH. Accordingly, a score of 0, no SAH or intra-ventricular hemorrhage (IVH) (very low risk for vasospasm); 1, focal or diffuse thin layer of SAH, no IVH (low risk for vasospasm); 2, focal or diffuse thin layer of SAH, IVH present (moderate risk for vasospasm); 3, focal or diffuse thick layer of SAH, no IVH (high risk for vasospasm); and 4, focal or diffuse thick layer of SAH, IVH present (highest risk for vasospasm).

3.10. **Data collection tools and procedures**

Data will be collected by neurosurgical residents in a prospectively. Each of the study populations will be followed on the scheduled time intervals outlined in the methodology and more often if there exist a clinical condition which is suspicious of the patient to develop the ischemic cerebral vascular complications. Data collection tool is prepared by using the google form and data will be filled case by case. The principal investigator will supervise and assure the completeness of data collected.

3.11. Data quality control

Two days intensive training will be given to the data collectors on how to conduct the data collection. Data quality will be managed by training and appropriate supervision of data collectors. Overall supervision will be made by the supervisor and principal investigator. And the collected data will be checked its completeness, clarity and accuracy. This quality checking will also be done daily after data collection and correction will be made before the next data collection measures. Data clean up, cross checking and double entry will be done before analysis.

3.12. Data processing and analysis

The coded data containing demographic, preop imaging factors, post op factors and post op control imaging factors will be exported to STATA version 17 statistical software for further management, cleaning and analysis. Descriptive statistics, frequencies and percentages for categorical variables and summary statistics for continuous data (mean with standard deviation in normally distributed data or median with IQR if the data is not normally distributed) will be used to characterize the study population. The normality distribution test will be done using the Kolmogorov-Smirnov test.

This outcome will be assessed in patients who underwent brain tumor surgery at the immediate postop, 3-4th post op day, 7-8th post op day, 12-14th post op day and 30th postop day.

The incidence rate will be calculated for the occurrence of cerebral vascular ischemic complication after brain tumor resection. Bivariable analysis will be done to see the association of each predictor variable with cerebral vascular ischemic complication. Variables with p-value of <0.25 in the bivariable analysis will be entered to multivariable analysis. The statistical significance will be

declared at p-value <0.05. The measure of association will be Risk Ratio (RR) with 95% confidence interval, for the study design is prospective followup study design.

Prediction model development: the occurrence function is written as; Incidence of cerebral vascular ischemic complication = f (Prognostic determinants (demographic factors, preop imaging factors, post op factors and post op control imaging factors)). The most important variables which can be ascertained early after the surgical procedure will be considered for the construction of prognostic model. The risk prediction model will be presented in the form of nomogram. We preferred nomogram because it has a user friendly graphical interface which can be used easly in the clinical practice.

The performance of the nomogram will be checked by assessing its discriminatory power and calibration. The discriminatory power of the model will be assessed using Area under the Curve (AUC). The AUC may range from 0.5 (no predictive ability) to 1 (perfect discrimination. Besides, the model calibration will be shown graphically by plotting the observed and predicted cerebral vascular ischemic complication. For the model calibration test, a value of P>0.05 will suggest a good model calibration (the model does not misrepresent the data). In the calibration plot, the more the points coincide with the 45-degree diagonal line, the better will be the model's calibration. The specificity and sensitivity will be determined for several cut-off values of the prediction probablities. Bootstrapping will be used for internal model validation. Models validated through this method are more stable. Hence, it is preferred over other methods of model validation like cross validation and split half method.

4. Ethical considerations

Ethical approval will be obtained from the Ethical Review Committee of Addis Ababa University. Confidentiality of the information will be assured by omitting personal identifiers like names. The research involves no more than minimal risk to the subjects and the waiver or alteration will not adversely affect the rights and welfare of the subjects.

5. Dissemination plan

The finding of this research will be shared to the neurosurgery unit so that it can serve as a baseline data to the attending neurosurgeons and fellow residents. Similarly, it will be presented in annual

neurosurgical society of Ethiopia and other international scientific conferences across the world. Last but not least, the finding of this research finding will be published in a reputable high impact neurosurgical journal so that its visibility and usefulness can be escalated in the scientific community.

6. Work plan

	Feb	Mar	Apr	May	Jun	July	Aug	Sep	Oct	Nov	Dec	Jan
Title selection												
Proposal writ												
Proposal presentation												
Data collection												
Data analysis												
Presentation of the finding												
Manuscript writing												
Submission for publication												

7. Budget break down

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