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Research Article

Neuroprotection Strategies for Patients Undergoing Neurosurgery for Supra- and Infratentorial Tumors: A Retrospective, Comparative and Quasi-Experimental Study

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Abstract

***Objective**: To evaluate neuroprotection strategies in supra- and infratentorial tumors in the period from 2018 to 2022 at the university hospital of Caracas.* ***Methods**: Retrospective, comparative and quasi-experimental study. It included 600 neurosurgical patients. The administration of pharmacological measures for brain protection and their adverse effects were evaluated.* ***Results**: the average age was 45.2 + 18.1 years, glioblastoma was statistically significant for supratentorial tumors and Schwannoma for infratentorial tumors. It was statistically significant the absence of drugs such as Vitamin C and Folic Acid in the years 2021-2022* ***Conclusions**: it was demonstrated that pharmacological measures, each and every one of them used, decrease and improve brain capacity, avoiding ischemia lesions and brain death.*

***Keywords**: neuroanesthesia, neuroprotection, tumors, supratentorial, infrantentorial, brain autoregulation, tumor.*

Introduction

The term "neuroprotection" is relatively new, but historical techniques with similar effects date back to ancient times, such as the use of hypothermia by Greek physicians for head trauma. Neuroprotection involves therapies aimed at preventing, delaying, or reversing cell death caused by neuronal injury, akin to cytoprotection methods seen in heart and blood vessel protection[1]. Furthermore, neuroprotection encompasses the organism's own protective responses post-trauma, which strive to preserve brain integrity and function[1-2].

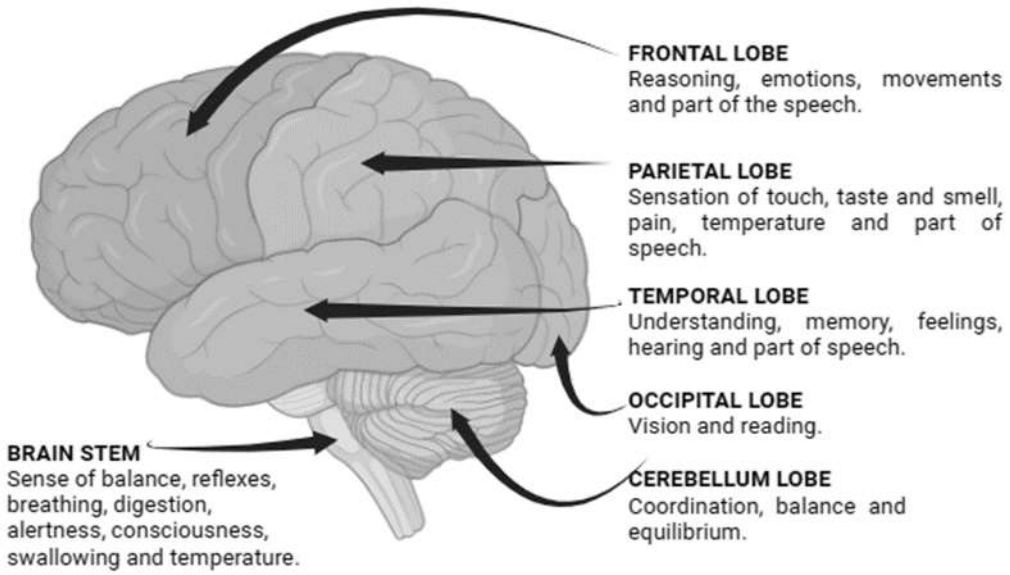
The management of neuroprotection involves both pharmacological and non-pharmacological approaches aimed at activating the brain's self-protection mechanisms, including the production of heat shock proteins, anti-inflammatory cytokines, endogenous antioxidants, and regulatory systems like GABAergic and cannabinergic pathways. The balance between these responses determines the outcome of tissue damage[1].

Perez et al, in 2019 defined brain tumors as abnormal masses growing within the brain. Primary tumors

originate within the brain itself, while secondary tumors, also known as metastatic tumors, arise elsewhere in the body and spread to the brain. The brain, protected by the skull and meninges, lacks lymphatic drainage and rarely disseminates through the bloodstream, making primary brain tumors unlikely to spread to other parts of the body[2].

Anatomically, the brain, comprising cerebral hemispheres, brainstem, cerebellum, and spinal cord, is encased in protective meninges. Together, these structures form the Central Nervous System (CNS), responsible for various mental functions such as memory, intelligence, speech, emotions, as well as sensory and autonomic functions like vision, taste, touch, hearing, breathing, and heart rate[2].

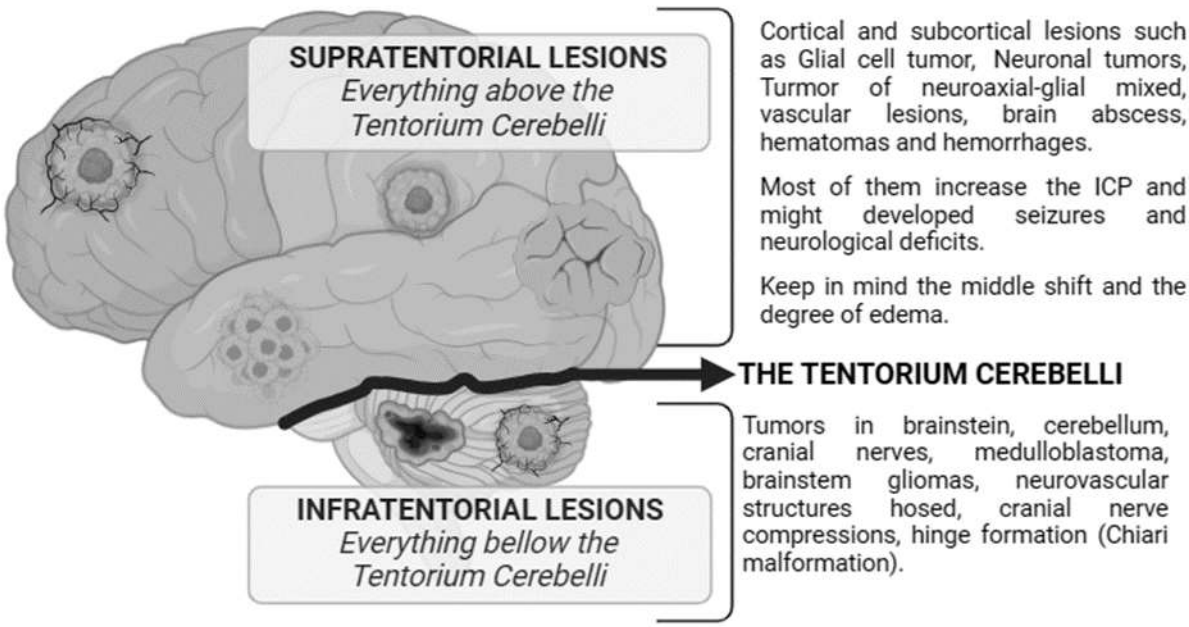
The brain is divided into two hemispheres connected by the corpus callosum, with four lobes controlling different functions: frontal lobe for reasoning, emotions, speech, and movement; parietal lobe for touch, pain, temperature sensation, and speech; temporal lobe for memory, hearing, and speech; and occipital lobe for vision[2.]



Brain tumors can be classified based on their location into three main areas: A) Supratentorial: These tumors primarily affect the cortical and subcortical brain structures located above the tentorium cerebelli. They are further subdivided into glial cell tumors, neuronal tumors, tumors of neuronal-glial-mixed origin, and embryonal tumors exhibiting characteristics of various lesions. B) Infratentorial: In this area, tumors affect structures located below the tentorium cerebelli, including the brainstem, cerebellum, and cranial nerves.

Tumors in this region include medulloblastomas and brainstem gliomas[3].

Infratentorial tumors are located in the lower back part of the brain, comprising the cerebellum and brainstem, while supratentorial tumors mainly involve cortical and subcortical brain structures above the tentorium cerebelli[3].



The ability to respond to stress is fundamental for all living organisms, as surviving a sub-lethal injury can lead to protection from subsequent lethal insults. This phenomenon, known as cerebral preconditioning or ischemic tolerance, is observed notably in the brain and heart. Pathophysiological aspects of brain ischemia/reperfusion include glutamate excitotoxicity, ATP consumption, disruptions in ionic homeostasis, and free radical formation[4].

Various substances such as anesthetics, hypothermia, sodium channel blockers, and ascorbic acid induce protection in the nervous system by acting on these mechanisms. Ischemic tolerance occurs in two time windows: early tolerance, involving membrane receptor adaptation within minutes to hours, and late tolerance, via gene activation and protein synthesis, lasting days[4].

The importance of cerebral protection is evident during cardiopulmonary resuscitation and surgeries requiring cerebral ischemia/hypoperfusion. Anesthesiologists can actively prepare the nervous system for such events to prevent injury[4].

Cerebral ischemia/reperfusion leads to profound neural metabolic alterations, including increased catabolism, ATP depletion, intracellular sodium accumulation, membrane potential alterations, and excitatory neurotransmitter action. Reperfusion initially supplies oxygen and glucose, leading to hyperglycemia and oxidative stress due to reactive oxygen species[4].

Antioxidants like vitamin C and E contribute to protection against free radicals. Inhibitory neurotransmitters like GABA and glycine regulate ion channels, mitigating ischemic damage. Severe alterations may lead to irreversible cell death when RNA transcription or DNA integrity is compromised[4].

Various substances such as anesthetics, hypothermia, sodium channel blockers, and ascorbic acid induce protection in the nervous system by acting on specific sites. Ischemic tolerance occurs in two distinct time windows: early tolerance, achieved through membrane receptor adaptation within minutes but declining rapidly within hours, and late tolerance, involving gene activation and protein synthesis lasting for days[4].

Cerebral protection's clinical relevance is evident during cardiopulmonary resuscitation and surgeries requiring maintenance of cerebral ischemia/hypoperfusion periods. Anesthesiologists can actively prepare the nervous system for ischemia-reperfusion events to prevent potential injury[4].

Complete cerebral ischemia or decreased cerebral flow followed by reperfusion leads to profound neural metabolic alterations, including increased catabolism, ATP depletion, intracellular sodium accumulation, membrane potential alterations, cell edema, and enhanced glutamate action. Reperfusion initially supplies excessive oxygen and glucose, leading to hyperglycemia exacerbating post-ischemic injury and oxidative stress due to reactive oxygen species[3-4].

Antioxidants like vitamin C and E, as well as inhibitory neurotransmitters like GABA and glycine, contribute to protection against free radicals and ion channel regulation, respectively. Severe alterations may lead to irreversible cell death when RNA transcription or DNA integrity is compromised[3-4].

Therapies targeting multiple inducers of neuroprotection are more effective than single-focus therapies. For instance, while MK-801 suppresses excitotoxic cell death, it may exacerbate apoptotic trauma[4].

The early phase of ischemic tolerance (up to 30 minutes after the insult) likely involves transmembrane flux-metabolic events, while the late phase (after 24 hours) involves genetic induction and protein synthesis. Besides sub-lethal ischemia, other conditions like hypothermia, hyperthermia, hypoglycemia, and pharmacological agents induce ischemic tolerance[4].

CHANGES DURING A BRAIN DAMAGE
Physiologically, normal cerebral flow in human is 50ml/100gr/min. It is considered to be critical when ranges between 15 to 20ml/100gr/min shown isoelectric EEG. When reaches 10ml/100gr/min loss of neuronal potential occurs leading deterioration of neurological functions.
Ischemia, due to decrease of cerebral flow increases cell metabolism, decreases ATP and Na+/K+/ADP and increases the intracellular Na+. Furthermore, alteration membrane potential causes edema as well as increases glutamate. Starts anaerobic glucose metabolism increasing lactate and thus more hydrogenous inside the cell.
Calcium ion, energy depletion and altered cell permeability allow Ca+ to enter through voltage-dependent-channel and by passive diffusion. Ca+ is considerably increases the cell damage.
Glutamate, it is an excitatory neurotransmitter which is involved in the production of ischemic damage. It activates NMDA receptors.
Free radicals, excerpt harmful effects on the CNS. Hydroxyl, peroxidase and superoxide increase the activation of phosphorylation under hypoxia in vascular beds and cell membranes leading more damage. Here is where the scavenger agents act.

Neuroprotective measures play a crucial role in preventing cognitive and motor decline in patients undergoing neurosurgical interventions. Both pharmacological and non-pharmacological approaches are recognized for their effectiveness in neuroanesthesiology, offering various mechanisms to prevent acute brain damage post-surgery.

In light of these benefits, researchers aimed to review neuroprotection measures used in supra- and infratentorial tumor surgeries at the University Hospital of Caracas between 2012 and 2022. Data were collected from patients undergoing tumor resection procedures at the Neurosurgery Service of the hospital, overseen by the Fellowship of Neuroanesthesiology.

Meanwhile, the Hospital of Neurosurgery "Manuel Velasco Suarez" in Mexico conducts a study focusing on the current state of neurosurgery and neuroanesthesiology practices. Their research aims to identify causes

of mortality in institutions performing such surgeries, informing decisions to enhance care, diagnosis, and treatment. Mortality rates serve as a critical metric for evaluating the effectiveness of existing protocols and guiding improvements in neurosurgical units worldwide[4].

Neuroprotection is defined as any preventive measure initiated before or alongside a hypoxic or ischemic insult to enhance neuronal tolerance and improve survival. It encompasses strategies aimed at shielding brain tissue from the detrimental biochemical, genetic, and molecular events triggered by ischemia. Neuroprotective treatment aims to intervene in the cascade of cellular events leading to cell death, including the release of excitatory neurotransmitters, calcium influx, and production of toxic products such as nitric oxide and free radicals[5].

The concept of a cerebral reperfusion window denotes the period following an ischemic event during which restoration of circulation can lead to total neurological function recovery. Within this window lies the neuroprotection window, where neuroprotective measures can mitigate or prevent brain damage caused by ischemia followed by reperfusion[5].

The University Hospital of Caracas (UHC) conducts a significant number of neurosurgical interventions, representing 20.2% of total surgeries, with 400 being elective procedures from 2018 to 2022. Brain protection measures during these procedures are crucial components of the neuroanesthesia protocol.

This research not only contributes positively to anesthetic practices, particularly in neuroanesthesiology, but also serves as a tool for preventing postoperative brain injury. It establishes protocols aimed at safeguarding neurosurgical patients at the UHC, benefiting the broader population undergoing such procedures. Thus, the importance of this study is justified by its potential impact on improving patient outcomes in neurosurgery.

Background

In Montero's study, the main cause of neuronal damage in the central nervous system (CNS) is identified as oxygen-glucose deprivation, which occurs in acute disorders such as ischemia, trauma, stroke, or neurodegenerative diseases, often encountered during anesthetic procedures. Both short-term (within 7 days) and long-term neuroprotection strategies are discussed, with intravenous agents shown to decrease cerebral metabolic rate, facilitate protein synthesis, enhance gabaergic activity, and exhibit antioxidant effects[6].

Dr. Leonardo Masri emphasizes the importance of implementing neuroprotection strategies in all types of anesthetic procedures to prevent cerebral hypoperfusion-related clinical manifestations. Understanding the

pathophysiology of acute neuronal damage is crucial, as ischemia plays a central role due to the brain's high metabolic activity and lack of energy reserves[7].

Prolonged ischemia leads to ATP depletion, anaerobic metabolism, lactic acid production, cytotoxic edema, free radical formation, and calcium influx through voltage-dependent channels, causing mitochondrial membrane dysfunction and neuronal damage. Excitatory amino acid neurotransmitters, particularly glutamate acting on NMDA receptors, exacerbate ischemic damage. Blockade of these receptors with substances like Ketamine, Dextromethorphan, Magnesium, and Zinc is used for brain protection, along with maintaining normal pH levels and scavenging free radicals to prevent CNS damage[7].

In Susan Porter's text on Neuroanesthesia from 2005, protocols in neuroanesthesiology are outlined with the following objectives:

1. Anesthesia in neurosurgery aims for gentle induction while maintaining stable hemodynamics, ensuring a correct operative field, and facilitating rapid awakening with the return of consciousness in the operating room.

2. Anesthetic agents should neither directly injure the brain by decreasing Cerebral Perfusion Pressure (CPP) nor indirectly increase brain volume.

3. Techniques should focus on reducing brain volume and Intracranial Pressure (ICP) by using intravenous anesthetics, mannitol, maintaining osmolarity, volemia, and proper blood pressure.

4. Optimal anesthetic care begins preoperatively with the evaluation of pulmonary function to prevent intraoperative hypoxia or hypercapnia, which can exacerbate brain swelling and complicate surgery, especially if there is an active pulmonary infection or if the patient has bronchogenic carcinoma.

5. Cardiovascular assessment is essential, as untreated arterial hypertension may predispose to cerebrovascular complications during the perioperative period, particularly after subarachnoid hemorrhage or traumatic brain injury.

6. Neurological examination should assess deficits, signs of intracranial hypertension, and the need for maintaining antiseizure treatment perioperatively, considering possible lower cranial nerve paralysis with posterior fossa tumors. Radiological examination with CT and MRI helps identify lesion location, edema, ventricular system alterations, and midline deviations indicating increased ICP.

7. Premedication, depending on the patient's neurological state and anxiety level, should involve

benzodiazepines rather than narcotics, with careful consideration before administering.

8. Anesthetic induction should be gentle, avoiding hypertensive responses to intubation and tension drops, using thiopental or propofol to decrease ICP while maintaining autoregulation and CO2 response.

9. Careful airway management is crucial, with fixation of the endotracheal tube to prevent displacement, particularly in patients positioned prone or sitting, ensuring hypoallergenic adhesive tape is used, and avoiding tapes around the neck to prevent venous obstruction.

10. Eye protection is necessary during head fixation, as painful stimulation may induce hypertensive responses similar to tracheal intubation.

11. Maintenance of anesthesia can be achieved through total intravenous anesthesia (TIVA) with propofol or inhalation anesthesia with isoflurane or sevoflurane, supplemented with fentanyl or remifentanil, with caution regarding the use of nitrous oxide due to its potential to decrease the minimum alveolar concentration (MAC) of other agents.

12. Controlled hyperventilation to reduce ICP is no longer the standard practice due to its negative effects on cerebral blood flow and cerebral metabolic demand, but if used, patients should be closely monitored to prevent cerebral ischemia, with consideration for increasing FiO2 to mitigate hyperoxemia also.

These protocols encompass various aspects of neuroanesthesia to ensure optimal patient outcomes during neurosurgical procedures.

To obtain a brain in good surgical conditions, there are a series of maneuvers that can help us to improve the operative conditions:

TENSE BRAIN DURING SURGERY MUST CHECK	
Head position and venous return	Slightly elevated the head
Proper ventilation (high peep increases the ICP). It is best monitoring the driving pressure instead.	Check EtCO2 and CO2, double check and compare with arterial blood gas. Aiming 32 to 35mmhg.
If the patient is on protoxide switch to total intravenous anesthesia with propofol as	Hypertonic saline solution or mannitol.

hypnotic.	
Cerebral spinal drainage.	Dexamethasone in the presence of malignant tumor.
Hydrate the patient with normal saline 0,9% instead of lactated ringer. Aiming serum Na+ above 145 mEq/L.	Control serum glucose and core temperature.

Supratentorial Lesions:

Various types of lesions such as tumors, vascular lesions, abscesses, and hematomas can occur in the supratentorial region, leading to symptoms such as elevated intracranial pressure (ICP), seizures, and neurological deficits. It is crucial to maintain adequate anesthesia induction, avoiding hypertensive responses to laryngoscopy and ensuring a stable hemodynamic state. Careful selection of anesthetic agents is necessary to avoid cerebral vasodilatation, hypoxia, hypercapnia, hypertension, and hypotension. Preoperative evaluation of pulmonary function is essential to prevent intraoperative complications related to brain swelling. Maintenance of normocapnia (PaCO2 between 32 and 35 mmHg) and normotension is recommended to avoid exacerbating brain injury. Mannitol or hypertonic sodium solutions can be administered for ICP reduction, and perioperative hydration with solutions devoid of glucose is preferred to avoid exacerbating cerebral edema. Continuous monitoring of vital signs, end-tidal CO2, urinary output, and precordial Doppler is necessary to detect and manage potential complications such as air embolism. Postoperative monitoring should include vigilant assessment for signs of intracranial hematoma, such as decreased level of consciousness or pupillary alterations[8].

Posterior Fossa Lesions:

The posterior fossa houses vital neurovascular structures and cranial nerves, making surgical access challenging and prone to complications such as air embolism. Lesions in this region include tumors, vascular lesions, cranial nerve compressions, and malformations. Patient positioning plays a crucial role in surgical access and anesthesia management, with options including supine decubitus with head rotation, supine

decubitus with head upright, lateral position, park bench position, and sitting position. Each position offers unique advantages and disadvantages in terms of surgical exposure, airway management, and risk of complications such as venous congestion, air embolism, and nerve injury. Careful fixation of the endotracheal tube and protection of peripheral nerves and vital organs are essential in each position to prevent intraoperative complications[8].

Overall, meticulous attention to patient positioning, anesthesia induction, intraoperative monitoring, and postoperative care is crucial in ensuring optimal outcomes for patients undergoing neurosurgical procedures involving supratentorial and posterior fossa lesions[8].|

Contraindications of the seated position

Absolutes

- Ventriculo-atrial shunt, ventriculo-peritoneal shunt - Persistence of the foramen ovale.
- Myocardial dysfunction.
- Pulmonary A-V fistula.

Related

- Functional hypotension
- In the preoperative assessment it is important to observe: Correct intravascular volume (hypovolemia facilitates gas embolism).
- Pre-existing lower-torque lesions that may be exacerbated after surgical manipulation and should be evaluated prior to extubation.
- Craniotomy of previous PF that may cause small mouth opening and intubation difficulties.
- Specific monitoring of posterior fossa surgery is aimed at detecting air embolism. In order of highest to lowest sensitivity will be: TEE, precordial Doppler
- End-tidal CO2 A multiperforated catheter should also be placed in the right atrium. The anesthetic objectives will be those of any neurosurgical intervention: adequate anesthetic depth, maintaining hemodynamic stability, optimizing surgical conditions and early awakening for a prompt neurological assessment. The induction agent will depend on the age and clinical conditions of the patient. It is

advisable to avoid propoxide since in case of air embolism it increases the size of the bubbles. Always maintain normoventilation [(8)].

- Avoid solutions containing glucose.

Hinge malformations

The approach to instability of the hinge and lesions involving the posterior part of the brainstem requires careful consideration of the underlying causes and anatomical considerations:

1. Instability of the Hinge: This instability can result from various causes including trauma, inflammation, metabolic disorders, or congenital abnormalities. Surgical approaches depend on the location and nature of the instability. Lesions involving the posterior part of the brainstem are typically approached posteriorly with the patient in a prone position. Conversely, anterior involvement may necessitate a transoral approach[8].

2. Chiari Malformations:

- Type I Chiari malformation involves descent of the cerebellar tonsils into the spinal canal, often accompanied by syringomyelia and hydrocephalus.

- Type II Chiari malformation entails herniation of the vermis and is typically associated with spina bifida and hydrocephalus.

3. Rheumatoid Arthritis: In cases of rheumatoid arthritis, anterior involvement is common, necessitating a transoral approach. Dislocations or compressions can occur due to ligament destruction or the presence of panus. Preoperative evaluation should include assessment for systemic changes associated with rheumatoid arthritis, such as cardiac valvular lesions, pulmonary fibrosis, anemia, renal impairment, and arthritis involving the arytenoid joints[8].

4. Airway Management: Airway management in these patients can be challenging due to restricted neck mobility, temporomandibular joint ankylosis, and immobilization devices such as a halo brace. Intubation may require the use of a fiberoptic scope, and tracheotomy may be indicated. Careful monitoring of spinal cord integrity is crucial during the procedure[8].

5. Intraoperative Complications: Intraoperative complications may include vascular injuries, cerebrospinal fluid fistulas, damage to lower cranial nerves, and air embolism.

6. Postoperative Considerations: Postoperatively, patients may experience significant edema of the posterior pharyngeal wall and inflammation of the arytenoids, which can compromise the airway. Close monitoring and prompt intervention may be necessary to manage these complications.

Overall, meticulous preoperative planning, careful surgical technique, and vigilant postoperative management are essential in addressing instability of the hinge and lesions involving the posterior part of the brainstem, particularly in the context of conditions such as Chiari malformations and rheumatoid arthritis[8].

The non-pharmacological approach to neuroprotective anesthesia

It involves the use of various agents and strategies to maintain neuronal integrity and reduce ischemic neuronal loss. Here is a summary of the key pharmacological measures:

1.Control of physiological variables: optimal control and maintenance of physiological variables such as blood pressure, oxygenation, ion balance, and CO2 exchange are paramount for neuroprotection. Brain monitoring tools, such as intracranial pressure monitoring (PPC), cerebral oxygen saturation (SjO2), brain tissue oxygen tension (ptiO2), near-infrared spectroscopy (NIRS), Doppler ultrasound, and electroencephalography (EEG), are essential for individualized optimization of these parameters based on the patient's pathology and needs.

2. Ventilatory Strategies: There is a classic controversy regarding the use of lung protective ventilation strategies, particularly in patients with neurological injuries. However, if the levels of positive end-expiratory pressure (PEEP) are lower than intracranial pressure and contribute to improving pulmonary distensibility, they may have a beneficial effect on cerebral perfusion by enhancing CO2 exchange and alveolar recruitment. Hypercapnia should be avoided as it is counterproductive in neurocritical patients[8].

3. Temperature Control: Fever has been shown to negatively impact the prognosis of patients with neurological injuries. Therefore, strict temperature control is essential to prevent hyperthermia and its associated complications. Additionally, maintaining normothermia has been linked to reduced intracranial pressure, decreased incidence of complications such as diabetes insipidus and seizures, and improved mortality rates[8].

4. Blood glucose control: There is debate regarding the optimal management of blood glucose levels in neurocritical patients. However, strict control of blood glucose has been associated with reduced intracranial pressure, fewer complications, and improved mortality rates compared to a more liberal approach. Moreover,

normoglycemia may also mitigate peripheral neuropathy, suggesting a protective effect on the peripheral nervous system[8].

In summary, the non-pharmacological approach to neuroprotective anesthesia involves meticulous control of physiological variables, ventilation strategies tailored to individual patient needs, strict temperature and blood glucose control, and utilization of brain monitoring tools to optimize cerebral perfusion and minimize ischemic neuronal damage.

The neuroprotection pharmacological approach to neuroprotective anesthesia

Corticosteroids

Its anti-inflammatory and membrane-stabilizing effect is known, as well as its effect on brain edema and its possible regenerative effect on the blood-brain barrier. However, there is only evidence of its neuroprotective efficacy in the case of peritumoral brain edema, especially metastatic; in baterial meningitis (especially in children) and in tuberculous meningitis (pending results in HIV populations). Two Cochrane Collaboration reviews have demonstrated the absence of protective efficacy in ischemic or hemorrhagic stroke. In trauma, the CRASH trial had to be stopped when 10000 patients had been included (half of those initially planned) because a significant increase in 14-day mortality was demonstrated in the group of patients treated with high doses of methylprednisolone. At 6 months the negative results for steroid-treated patients were maintained. In traumatic spinal cord injury, the NASCIS series of studies concluded with the following recommendation: "high doses of methylprednisolone (30 mg/kg over 30 minutes and 5.4 mg/kg/h) initiated early and for 24 to 48 hours can be used, knowing that the related complications outweigh the expected benefit of treatment". Furthermore, the use of corticosteroids constitutes an independent risk factor for the development of myopathy and neuropathy in the critically ill patient, suggesting a deleterious role at the level of the peripheral nervous system [8].

Neuroprotection is a challenge for the anesthesia and critical patient care professional, in which pathophysiological knowledge of ischemic injury (necrosis and apoptosis) is key to its understanding and application. Furthermore, it is a field in which the expectations created about some techniques or drugs have exceeded the reality of the final protective effect, so that the establishment of global clinical guidelines is a complex aspect. At present, we can affirm, based on the best scientific evidence, that correct hemodynamic and respiratory control of the neurological patient is key, supported by adequate brain monitoring, as well as

the prevention of hyperthermia and hyperglycemia. Hypothermia has a protective effect in diffuse injury secondary to cardiac arrest and seems to have a protective effect in selected groups of trauma patients (young people admitted hypothermic and probably in patients with intracranial hypertension refractory to conventional therapy). Anesthetics seem to be able to delay and attenuate ischemic injury, especially if it is of mild or moderate intensity, while corticosteroids have not been shown to be effective in traumatic, hemorrhagic or ischemic injury. Magnesium, in the absence of a large-scale trial, promises protective results in the prevention of vasospasm and late ischemia after subarachnoid hemorrhage, as do statins, although studies on the latter are still scarce. Both could soon constitute the appropriate therapy in association with nimodipine, which is already established in routine practice. Many other potentially effective agents for neuroprotection are at a preclinical research level [8].

Peritumoral brain edema at the molecular level is the result of disruption in the structure of the blood-barrier-brain (BBB). Of the three main cellular targets of glucocorticoids (tumor cells, endothelial cells, and astrocytes), protein expression in endothelial cells likely play the most critical role in glucocorticoids-mediated reversal of peritumoral brain edema. In particular, the tight junction proteins occluding, claudin-5, and zonula occludends-1 along with matrix-metalloproteinase and Vascular Endothelial Growth Factors (VEGF) are central to the glucocorticoids mechanism of action. Importantly though, in vitro studies can often be at odds with clinically relevant mechanisms. It has developed an in vivo animal model which isolates VEGF-mediated vasogenic edema and plan to employ this model in further elucidation of mechanism of glucocorticoid action. A better understanding of these glucocorticoid mechanisms will help identify novel targets for edema resolution potentially with better side effect profiles than glucocorticoids.

Charissa A. C. Jessurun and Cols. Published in 2019 a systematic search that was performed in PubMed, Embase, Web of Science, Cochrane, Academic Search Premier, and PsycINFO to identify studies that reported edema volume reduction, symptomatic relief, adverse events and survival in relation to dexamethasone dose in glioma or brain metastasis (BM) patients and after screening 1812 studies, fifteen articles were included for qualitative review. Most studies reported a dose of 16 mg, mostly in a schedule of 4 mg four times a day [18].

At the Hospital University of Caracas, we usually use a loading dose of 16mg /kg and then 4mg every six hours. Nevertheless, those patients that are already on dexamethasone we just continue the therapy without a loading dose.

Lidocaine

A drug that belongs to the class of amide local anesthetic. Its effect on cerebral metabolism can explain the effect of intravenous lidocaine on brain relaxation after dura opening. In mammal experiments done by Astrup et al, lidocaine infusion resulting in flat electroencephalogram concluded that spontaneous electrocortical activity is abolished by lidocaine, similar to barbiturate action [9,10.] The abolition of electrocortical activity reduces 60% of energy consumption or brain metabolism[15]. In addition, lidocaine also affects Na-K leak fluxes. From the experimental model, in the ischemic brain, the Na-K ion pump fails to maintain homeostasis due to energy depletion, resulting in Na ion leaks into and K ion out of cell passively following electrochemical gradient and membrane permeability. The grade of ion K leaks outside the brain cell can be measured by microelectrodes inserted into the surface of the brain cortex. After lidocaine infusion, ion K leaks outside brain cells are reduced and slowed, indicating that lidocaine reduces Na-K exchange leak fluxes. The effect of reducing ion leak fluxes is also seen in hypothermia but not in thiopental, indicating lidocaine, not thiopental, has a membrane-sealing effect[9]. This membrane sealing effect (membrane stabilization) is related to energy to maintain cellular integrity that accounts for 40% of brain metabolism.[19] In this experiment, Astrup et al also measured the effect of lidocaine on $CMRO_2$ and cerebral metabolic rate for glucose (CMRgluc) by the sagittal sinus outflow method that allows continuous measurement of oxygen and glucose consumption. The result is that lidocaine can reduce $CMRO_2$ and CMRgluc when given alone and after thiopental infusion. This effect is specific to lidocaine, supporting the hypothesis that lidocaine can block Na-K leak fluxes and oxygen and glucose consumption for active ion transport.(9) Based on these experimental results, lidocaine can reduce cerebral metabolism by inhibiting synaptic transmission and membrane sealing effect that reduces ion transport demand.(9) Sakabe et al also studied lidocaine effect on cerebral metabolism in mammal experimental using a lower dose of lidocaine and have the similar result that lidocaine can decrease $CMRO_2$ significantly[11].

Furthermore, lidocaine can reduce CBF due to decreased cerebral metabolism and cerebrovascular vasoconstrictor properties[12]. Lam et al study in humans during normocapnia and hypocapnia support this postulate based on data that lidocaine infusion 5 mg/kg loading dose over 30 minutes followed by infusion of 45 μg/kg/min in normocapnia patient can reduce CBF and $CMRO_2$ by 24% and 20% respectively[13]. In Grover et al; Studied, 1.5 mg/kg lidocaine loading dose can decrease ICP by reducing cerebral blood volume and cerebral metabolism. Based on data supporting the hypothesis, lidocaine can reduce cerebral metabolism and CBF, it can explain its effect on brain relaxation after dura opening during craniotomy surgery[17].

In the surgeon's satisfaction outcome, the proportion of very satisfied and satisfied surgeons in the lidocaine group was 70% and 26.7%, respectively. In contrast, in the placebo group, it was 10% and 60%, respectively ($P < .001$). Further analysis between surgeon's satisfaction and brain relaxation when the dura opens found that 100% of the surgeon is very satisfied and satisfied is when the brain relaxation is good. Based on our knowledge, currently, there is no validated checklist or surgeon's satisfaction questionnaire yet, so this study assesses surgeon's satisfaction intraoperatively by subjectively evaluating the surgeon using a satisfaction scale.

In our institution we use a protocol that consists a loading dose during the anesthetic induction of 1,5mg/kg/bolus and then starts an infusion pump of 2mg/kg/h, then it is turn off when the surgeon ends the closing of the dura.

Magnesium sulfate

Magnesium is neuroprotective that enhances neuronal survival by inhibition of excitatory glutamate release, blockade of NMDA glutamate receptors, and regulation of regional cerebral blood flow by vascular smooth muscle relaxation, subsequently increasing cerebral blood flow in the ischemic region. Several studies have documented that the serum magnesium level decreases after traumatic brain injury and magnesium supplementation, whether given before or shortly after injury, improves the neurological outcome in animals with brain injury and artificially lowered magnesium concentrations. S100B is a well-studied biomarker of brain injury. It is a low-molecular-weight calcium-binding protein most abundant in the CNS. Neuron-specific enolase (NSE) is an isoenzyme of enolase in the glycolytic cascade. Together with S100B, NSE is a specific tissue factor of brain injury. The levels of both proteins have been reported to increase after TBI, stroke, and subarachnoid hemorrhage. The increase in serum levels of these proteins has been shown to be related to the intensity of brain injury and clinical outcome. [(18)] Magnesium sulfate also improves cerebral vasoconstriction, inhibiting calcium channels, and at the same time in its pharmacological properties it is a membrane stabilizer, reducing free radicals; at a dose of 30 mg/kg/day[8].

As a protocol we use a loading dose of 30mg/kg/bolus. In some cases, we set an infusion pump with a maintenance of 6 – 20mg/kg/h with a serum sulfate lower than 2.5mg/dL.

Ascorbic acid

Ascorbic acid (vitamin C) occurs physiologically as the ascorbate anion: a water-soluble antioxidant that is found throughout the body. However, despite the high, homeostatically regulated levels of brain ascorbate, its specific functions in the CNS are only beginning to be elucidated [(19)]. Certainly, it acts as part of the intracellular antioxidant network, and as such is normally neuroprotective. There is also evidence that it acts as a neuromodulator. A possibly unique role it might have is as an antioxidant in the brain extracellular microenvironment, where its concentration is modulated by glutamate–ascorbate heteroexchange at glutamate uptake sites [(19)]. Ongoing studies of ascorbate and glutamate transporters should lead to rapid progress in understanding ascorbate regulation and function the high intracellular concentration of ascorbate in neurons suggests that it is has a significant role in normal neuronal physiology[20]. Given the well-established characteristics of ascorbate as an electron donor and free-radical scavenger, it is likely that this role comes from neuroprotective actions as a component of the neuronal antioxidant network. The fact that ascorbic acid is regulated homeostatically, but modulated by glutamate-mediated activity, suggests that the extracellular compartment is an important site for ascorbate neuroprotection. Ongoing advances in research on ascorbate and glutamate transporters should lay the groundwork for rapid increases in our understanding of ascorbate regulation in the brain[19].

Ascorbic acid is a key antioxidant of the CNS. Under brain activity, ascorbic acid is released from glial reservoirs to the synaptic cleft, where it is taken up by neurons. In neurons, ascorbic acid scavenges reactive oxygen species (ROS) generated during synaptic activity and neuronal metabolism where it is then oxidized to dehydroascorbic acid and released into the extracellular space, where it can be recycled by astrocytes. Other intrinsic properties of ascorbic acid, beyond acting as an antioxidant, are important in its role as a key molecule of the CNS[20]. Ascorbic acid can switch neuronal metabolism from glucose consumption to uptake and use of lactate as a metabolic substrate to sustain synaptic activity. Multiple evidence links oxidative stress with neurodegeneration, positioning redox imbalance and ROS as a cause of neurodegeneration[20].

Manuel Suter and Cols. Published in 2022 a systematic review where studied the efficacy and safety of perioperative vitamin C in patients undergoing noncardiac surgery, in this study they analyzed 37 researches where 2747 patients were included with a homogeneous population and concluded that the effects on morbidity and mortality are inconclusive and mostly uninvestigated. A small reduction in postoperative pain was found. Adverse events were rare but not systematically assessed. The evidence is uncertain, not supporting the use of vitamin C outside an experimental setting[21].

Nevertheless, recommended dosage ranges between 1g to 5g even there are studies in aesthetic practice that high dose up to 14gr IV seems to be safe. As neuroprotection most used doses go from 1 to 5gr and in our center we administer 2gr IV in bolus as loading dose. The, it it is continued at the PACU or ICU in the hydration drips.

Mannitol

The risk of brain swelling after dural opening is high in patients with midline shift undergoing supratentorial tumor surgery. Brain swelling may result in increased intracranial pressure, impeded tumor exposure, and adverse outcomes. Mannitol is recommended as one of the first-line dehydration treatment to reduce brain edema and enable brain relaxation during neurosurgery. Research has indicated that mannitol enhanced brain relaxation in patients undergoing supratentorial tumor surgery; however, these results need further confirmation, and the optimal mannitol dose has not yet been established[22].

Higher osmotic pressure in the blood vessels after the infusion of mannitol drives water molecules from the brain tissue to blood vessels and results in brain tissue dehydration. However, the role of mannitol in reducing brain edema depends on an intact blood–brain barrier (BBB). If the BBB is damaged, mannitol will extravasate outside the blood vessels and will transfer water molecules into brain tissue, which will aggravate cerebral edema and increase intracranial pressure. There may be some degree of BBB disruption in certain patients, which would prevent the desirable effects of mannitol; however, the extent of this disruption is unclear and often affected by multiple-dose mannitol. The use of mannitol for the type of surgery that patients in our study will undergo has been found overall to be beneficial; however, the appropriate dose of mannitol is controversial, particularly since large multiple doses can have negative effects[22].

There are many protocols of dosage even trails and guidelines for stroke and BTI. Most of the studies are inconclusive because renal and side effects as well as electrolytes disturbances in the postoperative period[8]. Yummin Peng and Cols. Published a randomized controlled where assessed the effect of mannitol on intraoperative brain relaxation in patients undergoing supratentorial tumors. The study included 220 patients and administered 20% mannitol of 0,7, 1.0, and 1,4g/kg respectively at a rate of 600ml/h. The outcomes shown that the higher dose of mannitol the faster onset of brain dehydration but the more undesirable postoperative effects. However, a loading dose of 1gr/kg was safe with negligible effects on the internal environment. So, the most common dose is at of 0.5 to 1 g/kg. It has a half-life of 2 to 3 hours and the

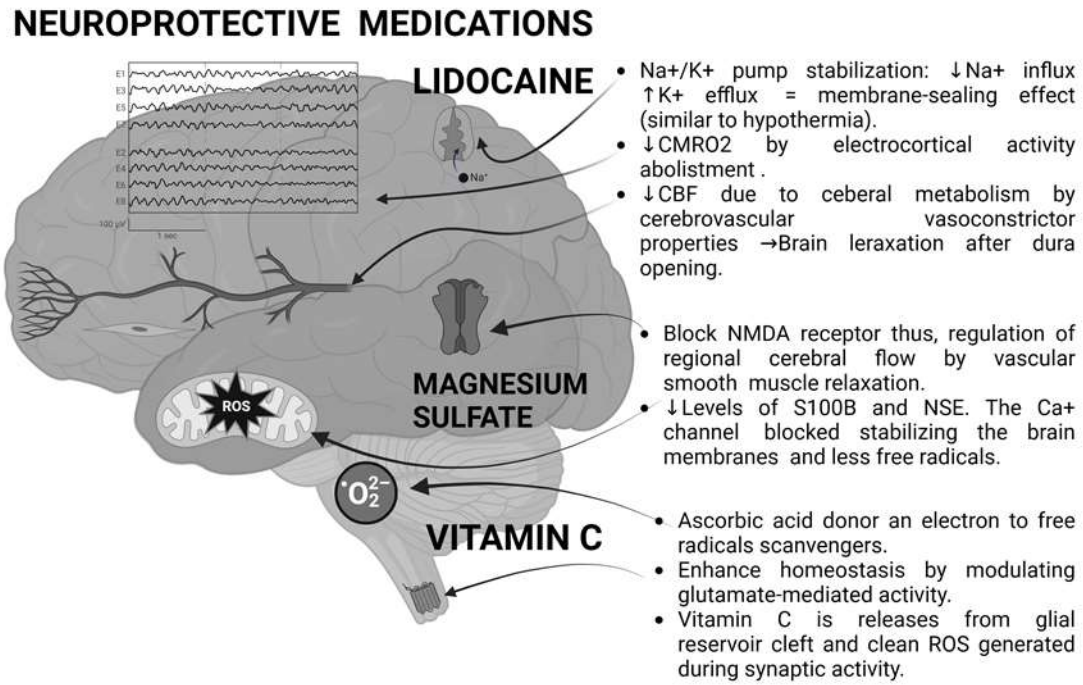
maximum hyperosmotic effect is at 36 minutes [(22)]. In the practice of neuroanesthesia as a measure of neuroprotection improves circulation, with studies reporting that it reduces cerebral edema with decreased cerebral blood flow; at doses of 0.25mh/kg/dose[8].

Hypertonic Solutions

Many studies have searched for alternative hypertonic solutions with different concentrations for brain relaxation in neurosurgery, of which the hypertonic saline (HS) is the most popular one. The administration of HS initially decreases hematocrit and blood viscosity and increases cerebral perfusion, and eventually, it results in the reduction of ICP and brain's blood volume and finally leads to brain relaxation. In addition to the mentioned properties of HS, it appears to have anti-inflammatory and neuroprotective effects, which has been studied in several studies in recent years. Furthermore, researchers tend to measure specific neural biomarkers to estimate the intensity of brain injury in patients suffering from brain pathologies. S100B is a known marker of neural cell damage which is specific to brain injury. Serum levels of this biomarker have been shown to increase among patients with brain tumor and traumatic brain injury, and it has been reported to correlate with cerebral perfusion pressure and neural integrity. Although many studies have evaluated HS for the management of raised ICP (RICP) in patients with acute and chronic RICP in the intensive care unit (ICU), only a few studies have evaluated the effectiveness of HS in brain relaxation of the patients undergoing elective surgery for brain tumors. Farhad Etezadi and cols. Compared preoperative HS versus mannitol for intraoperative brain relaxation and early postoperative outcomes and concluded that HS infusion just before the onset of craniotomy is at least as effective as mannitol in controlling intraoperative brain edema in patients with supratentorial glioma. Improved early postoperative course and lower degrees of S100B rise after craniotomy[23].

In 2007, Rozet et al. compared the effects of mannitol and hypertonic saline on intraoperative brain relaxation in 40 patients undergoing elective craniotomy and found a similar effect in both treatment groups. However, the intracerebral pathology of the patients in this study varied widely, and only six of the ten patients with supratentorial brain tumors received mannitol. Additionally, the preoperative peritumoral edema and intracranial pressure were not recorded, and only a single dose of mannitol (1g/kg) was administered. Wu et al. compared the effects of 160 mL of 3% hypertonic saline and 150 mL of 20% mannitol on brain relaxation. Their study suggested that 3% hypertonic saline provided better relaxation; however, the lengths of hospital and intensive care unit stays did not significantly differ[23].

As protocol for our neurosurgical cases we use a dose of HS of 4ml/kg/bolus at 3%, 3,5% or 7% respectively. Aiming a serum Na+ over 145mEq/L.



General objective

To analyze the use of neuroprotection measures in supra- and infratentorial tumors in the period 2018-2022 at the University Hospital of Caracas.

Specific objectives

1. To compare brain protection measures from 2018-2022 in neurosurgical patients.
2. To record the use of neuroprotective drugs in the transoperative management of neurosurgical patients with supratentorial and infratentorial tumors for each year.
3. To analyze arterial blood gases as a reference value for neuroprotection.
4. To determine which age group, gender, was the most prevalent for neurosurgical surgeries.

5. Identify the presence of adverse effects and drug failure for drugs used as neuroprotectants for each year.

Ethical aspects

Patients who were programmed for scheduled and emergency exeresis of supra- and infratentorial tumors at the University Hospital of Caracas, who were administered pharmacological and non-pharmacological brain protection measures during the period 2018-2022. pre-anesthetic assessment was performed to estimate inclusion and exclusion criteria for patients

The data collected in this research are confidential and were used only for this purpose.

Methods

Type of study Retrospective, comparative and quasi-experimental study.

Population and sample

The population studied was represented by all those patients who attended the Neurosurgery service scheduled for exeresis of supra- and infratentorial tumors during the period from 2018 to December 2022. According to data provided by the Department of Statistics of the University Hospital of Caracas (statistics section), for the period 2018-2022 a total of 600 patients underwent Neurosurgical operations, of which 400 underwent supra- and infratentorial Tu exeresis electively, and 200 patients on an emergency basis. Based on these data, considering a confidence level of 95%, and accepting an error of 5%, the sample consisted of 34 patients, which was computed using the calculator at: http://www.med.unne.edu.ar/biblioteca/calculos/calculadora.htm.

The inclusion and exclusion criteria used in the study are as follows:

Inclusion criteria:

- Ages 18- 70 years

Exclusion criteria:

- Spinal pathology
- Allergy to NSAIDs
- Allergy to the drug under study or its derivatives.

Procedure

The procedure for patients scheduled for exeresis of supra and infratentorial tumors involves several steps aimed at ensuring comprehensive evaluation, proper preoperative preparation, anesthesia induction, intraoperative monitoring, and postoperative care. Here's a breakdown of the procedure:

1. Pre-anesthetic Visit:

- Patients scheduled for surgery undergo a pre-anesthetic visit where a detailed physical examination is conducted.

- Demographic and clinical data are collected, including comorbidities, personal history, characteristics of the tumor lesion, and relevant paraclinical data.

- Inclusion and exclusion criteria are applied to assess the patient's suitability for surgery.

2. Preoperative Preparation:

- One hour before surgery, in the pre-anesthetic area, patients receive subcutaneous infiltration of 1 ml of 1% lidocaine for local anesthesia.

- Two peripheral venous lines are catheterized with 18 or 20 G caliber endovenous catheters, each connected to a hydration system with a macro drip and a 500 ml 0.9% sodium chloride solution.

- Pre-anesthetic medication is administered via one of the venous lines, which includes Ketoprofen 100mg or Dipyrone 1g, Ranitidine 50mg, Metoclopramide 10mg, Dexamethasone 8 mg, vitamin C 1 gram, and antibiotic therapy if no allergy is reported.

3. Intraoperative Monitoring:

- Monitoring is performed with three-lead electrocardiography (EKG), noninvasive arterial pressure (PANI), and pulse oximetry (SpO2) to ensure patient safety during anesthesia.

- Anesthesia induction is carried out according to the patient's medical records, either with General Balanced Anesthesia or Total Intravenous Anesthesia (TIVA).

4. Surgery:

- The surgery for exeresis of supra and infratentorial tumors is performed according to the planned procedure.

- Pharmacological measures may be administered intraoperatively as deemed necessary based on patient response and surgical requirements.

5. Postoperative Care:

- After surgery, patients are transferred to the Post-Anesthesia Care Unit (PACU) for monitoring and recovery.

- Data regarding pharmacological measures and postoperative management are recorded by the researcher through review of clinical records.

Overall, this procedure ensures comprehensive care for patients undergoing tumor resection surgery, including thorough evaluation, appropriate preoperative preparation, meticulous intraoperative monitoring, and attentive postoperative management to optimize patient outcomes and safety.

Appropriate statistical treatment

In order to achieve the proposed objectives, the statistical analysis of the data was performed as follows:

- The data are presented in tables and graphs, according to the type of variable and the information collected.
- Descriptive statistics were obtained for the variables under study, for the qualitative variables the absolute frequencies and percentages of each modality, while for the quantitative variables, the minimum, maximum, arithmetic mean and standard deviation values were obtained. For the comparison between the study groups, hypothesis contrasts were performed, also according to the type of variable. Thus, for the qualitative variables the chi-square contrast was applied, while for the quantitative variables the hypothesis contrast was applied for the differences of means (Student's t), both contrasts were performed at a confidence index of 95%, with a significance level of 5%, where it was affirmed or not, that the two

groups were significantly different in relation to their degree of analgesia if a p-value of less than 0.05 was obtained.

Results

600 patients were included in the study period, whose average age was 45.2±18.1 years, per year 150 surgeries were included in each year (2018, 2019 and 2020) then it is observed that there was a reduction of intervened cases in the year 2021 (90 cases) and by 2022 decreases to 60 cases (Table 1).

Table 2 shows the distribution of brain tumors according to their histological excision, where glioblastoma was the pathology that significantly predominated in supratentorial tumors (p=0.008), while in infratentorial tumors Schwannomas predominated in all study years (p <0.001).

By sex there was no predominance of tumor location, except in 2017 (p=0.004) and 2018 (p=0.02) in the female sex which accounted for the majority of supratentorial tumors (Table 3).

Table 4 and 5 show the drugs used in neuroanesthesia, where it is observed that in 2020 and 2021 there was a statistically significant decrease (p<0.000000001) in the use of these drugs for anesthesia.

Regarding the failure of drugs used in neuroanesthesia, it was found that there was reported failure of more than 60% in 2021 and 2022 of vitamin C and folic acid (p<0.000000001). Table 6.

There were no statistically significant differences in gasometric behavior reported during the different years of the studies in terms of gasometric improvement or worsening (Table 7).

Table 8 shows that patients undergoing supratentorial surgery have a urinary volume of 200 to 500 cc in the first hour and the same is significantly increased (p<0.001) at the third hour after initiation of anti-edema measures.

Discussion and Summary

From the demographic point of view, 600 patients were included for the study, both study groups were homogeneous in terms of age, so it can be said that the groups are comparable and that these characteristics do not influence the observed results, the average age of the two groups being 45.2 + 18.1 (1 see table 1)

Referring to the annual distribution of supra- and infratentorial tumors according to their histology in patients

undergoing cranial surgery from the period 2018-2022, where in supratentorial tumors gliobastoma was the most predominant pathology with a p value > 0.008. And in infratentorial tumors, it was statistically significant Schwannoma with a p value < 0.001 (1 see table 2).

Analyzing the predominance by sex in supra- and infratentorial pathologies, it is evident that in 2007 it was statistically significant with a value of p < 0.004 for the female sex (see table3) .

It was further demonstrated that, in the analysis of years, there was a statistically significant difference in drugs in neuroanesthesia in 2020 and 2021 with a p-value < 0.0001 (see table 4) .

It is evident that there were no statistically significant differences in the gasometric control with the pharmacological controlled measures. If there were statistically significant differences with p value < 0001 in terms of diuresis with the use of mannitol in the years 2018- 2020 at the first hour and at the third hour (see table5.6.7.8)

From the results obtained in this Special Degree Project, the researcher concludes that all pharmacological and non-pharmacological measures for neuroprotection are of vital importance to apply them, because with this we prevent acute and perhaps chronic injuries with an adequate use of them.

The study was limited by the fact that it was conducted in a continuing education center that evaluates the learning curve.

They also recommend increasing the sample size in order to decrease the sampling error, as well as recording and evaluating hemodynamic variables, which will allow the results to be extrapolated to the general population. Evaluation of anthropometric measurements.

Table 1. Annual characteristics of the patients who underwent neurosurgical intervention.

Sample characteristics	**N=600**	
Age (years) mean ± SD	45,2	18,1
Surgeries of 2016	150	25,0%
Surgeries of 2017	150	25,0%
Surgeries of 2018	150	25,0%
Surgeries of 2019	90	15,0%
2020 Surgeries	60	10,0%

Source: Clinical Histories of the Department of Statistics of the HUC. Min: Minimum Max: Maximum SD: Standard Deviation.

Table 2. Annual distribution of supra- and infratentorial tumors according to histology. In patients who underwent cranial surgery.

Supratentorial Tumors	**Year**					**p* value**
	2018 (n/%)	**2019 (n/%)**	**2020 (n/%)**	**2021 (n/%)**	**2022 (n/%)**	
Astrocytomas	10 (11,5%)	15 (14,2%)	10 (10,0%)	8 (13,6%)	5 (16,7%)	**0,008**
Meningioma	15 (17,2%)	20 (18,9%)	20(20,0%)	6 (10,2%)	5 (16,7%)	
Oligodendroglioma	8 (9,2%)	5 (4,7%)	18 (18,0%)	7 (11,9%)	0 (0,0%)	
Glioblastoma	34(39,0%)	45 (41,4%)	42 (42,0%)	25 (42,4%)	17 (56,7%)	
Anaplastic astrocytoma	10 (11,5%)	13 (12,3%)	9 (9,0%)	9 (15,3%)	2 (6,7%)	
Lymphomas	10 (11,5%)	8 (7,5%)	1 (1,0%)	4 (6,8%)	1 (3,3%)	
Infratentorial Tumors	**Year**					**p* value**
	2018 (n/%)	**2019 (n/%)**	**2020 (n/%)**	**2021 (n/%)**	**2022 (n/%)**	
Astrocytoma grade II	9 (14,3%)	4 (9,1%)	13 (26,0%)	7 (14,3%)	4 (13,3%)	**<0,001**
Pilocytic astrocytoma	13 (20,6%)	8 (18,2%)	11 (22,0%)	5 (10,2%)	6 (20,0%)	
Anaplastic astrocytoma	2 (3,2%)	5 (11,4%)	8 (16,0%)	6 (12,2%)	1 (3,3%)	
Subpendinoma	15 (23,8%)	7 (15,9%)	4 (8,0%)	3 (6,1%)	0 (0,0%)	
Hemagioblastomas	2 (3,2%)	1 (2,3%)	9 (18,0%)	9 (18,4%)	9 (30,0%)	
Meningioma	6 (9,5%)	3 (6,8%)	1 (2,0%)	4 (8,2%)	0 (0,0%)	
Schwannoma	16 (25,5%)	16 (36,4%)	4 (8,0%)	15 (30,6%)	10 (23,4%)	

*$\chi 2$ test

Source: Clinical Histories of the HUC Statistics Department

Table 3: Annual distribution according to sex in patients with supra- and infratentorial tumors submitted to cranial surgery.

Year	Location of tumors	Sex				Total		p* value
		Female		Male				
		N	%	N	%	N	%	
2018	Supratentorial tumors	50	57,5	37	42,5	87	58,0	0,81
	Infratentorial tumors	35	55,6	28	44,4	63	42,0	
2019	Supratentorial tumors	80	75,5	26	24,5	106	66,3	**0,004**
	Infratentorial tumors	28	51,9	26	48,1	54	33,8	
2020	Supratentorial tumors	50	50,0	50	50,0	100	66,7	**0,02**
	Infratentorial tumors	35	70,0	15	30,0	50	33,3	
2021	Supratentorial tumors	30	60,0	20	40,0	50	55,6	0,39
	Infratentorial tumors	20	50,0	20	50,0	40	44,4	
2022	Supratentorial tumors	20	66,7	10	33,3	30	50,0	0,29
	Infratentorial tumors	15	50,0	15	50,0	30	50,0	

*Fisher's test

Source: Clinical Histories of the HUC Department of Statistics.

Table 4: Distribution of neuroprotective drugs used in supratentorial tumors by year.

Neuroprotective drugs	SUPRATENTORIAL TUMORS									
	Year 2018		Year 2019		Year 2020		Year 2021		Year 2022	
	N (87)	%	N (106)	%	N (100)	%	N (50)	%	N (30)	%
Dexamethasone	87	100,0	106	100,0	90	90,0	35	70,0	30	100,0
Hydrocortisone	87	100,0	106	100,0	97	97,0	30	60,0	25	83,3
Ranitidine	87	100,0	106	100,0	87	87,0	45	90,0	30	100,0
Metoclopramide	87	100,0	100	94,3	100	100,0	50	100,0	30	100,0
Vitamin C	87	100,0	90	84,9	89	89,0	10	20,0	10	33,3
Folic acid	87	100,0	106	100,0	89	89,0	10	20,0	10	33,3
Lidocaine	87	100,0	106	100,0	95	95,0	40	80,0	30	100,0
MgSo4	87	100,0	90	84,9	94	94,0	30	60,0	30	100,0
Dipyrone	87	100,0	90	84,9	80	80,0	40	80,0	25	83,3
Mannitol	60	69,0	80	75,5	90	90,0	30	60,0	30	100,0
Hypertonic Solution	27	31,0	90	84,9	50	50,0	15	30,0	15	50,0

$\chi 2=396$; degrees of freedom=40 ; $p<0.000000001$ value.

Source: Clinical Histories of the HUC Statistics Department.

Table 5: Distribution of neuroprotective drugs used in infratentorial tumors by year.

Neuroprotective drugs	INFRATENTORIAL TUMORS									
	Year 2018		Year 2019		Year 2020		Year 2021		Year 2022	
	N (63)	%	N (44)	%	N (50)	%	N (40)	%	N (30)	%
Dexamethasone	63	100,0	44	100,0	50	100,0	20	50,0	30	100,0
Hydrocortisone	63	100,0	44	100,0	48	96,0	30	75,0	25	83,3
Ranitidine	63	100,0	44	100,0	50	100,0	40	100,0	30	100,0
Metoclopramide	63	100,0	44	100,0	50	100,0	40	100,0	30	100,0
Vitamin C	63	100,0	30	68,2	45	90,0	10	25,0	10	33,3
Folic acid	63	100,0	30	68,2	30	60,0	10	25,0	15	50,0
Lidocaine	63	100,0	44	100,0	47	94,0	30	75,0	20	66,7
MgSo4	63	100,0	40	90,9	40	80,0	30	75,0	20	66,7
Dipyrone	63	100,0	20	45,5	45	90,0	35	87,5	26	86,7
Mannitol	33	52,4	30	68,2	45	90,0	35	87,5	26	86,7
Hypertonic Solution	30	47,6	30	68,2	30	60,0	30	75,0	10	33,3
$\chi 2=286$; degrees of freedom=40 ; $p<0.0000001$ value.										

Source: Clinical Histories of the HUC Statistics Department.

Table 6: Distribution of neuroprotective drugs used in infratentorial tumors by year.

Neuroprotective drugs	Drug failure per year									
	Year 2018		Year 2019		Year 2020		Year 2021		Year 2022	
	N (150)	%	N (150)	%	N (150)	%	N (90)	%	N (60)	%
Dexamethasone	0	0,0	0	0,0	10	6,7	35	38,9	0	0,0
Hydrocortisone	0	0,0	0	0,0	5	3,3	30	33,3	10	16,7
Ranitidine	0	0,0	0	0,0	13	8,7	5	5,6	0	0,0
Metoclopramide	0	0,0	6	4,0	0	0,0	0	0,0	0	0,0
Vitamin C	0	0,0	30	20,0	16	10,7	70	77,8	40	66,7
Folic acid	0	0,0	14	9,3	31	20,7	70	77,8	35	58,3
Lidocaine	0	0,0	44	29,3	8	5,3	20	22,2	10	16,7
MgSo4	0	0,0	20	13,3	16	10,7	30	33,3	10	16,7
Dipyrone	0	0,0	40	26,7	25	16,7	25	27,8	9	15,0
Mannitol	0	0,0	40	26,7	15	10,0	25	27,8	4	6,7
Hypertonic Solution	0	0,0	30	20,0	70	46,7	55	61,1	35	58,3

$\chi 2=270$; degrees of freedom=30 ; $p<0.0000001$ value.

Source: Clinical Histories of the HUC Statistics Department.

Table 7: Behavior of arterial blood gases in patients with brain tumors who underwent surgery according to the year**.**

GSA parameter	Brain tumors										p* value
	2018		2019		2020		2021		2022		
	1°hour	3rd hour	1°hour	3rd hour	1°hour	3rd hour	1°hour	3rd hour	1°hour	3rd hour	
FiO_2	0,5±0,2	0,5±0,1	0,5±0,1	0,5±0,1	0,5±0,1	0,5±0,1	0,5±0,1	0,5±0,1	0,5±0,1	0,5±0,2	0,90
pH	7,43±0,09	7,48±0,02	7,40±0,09	7,52±0,08	7,53±0,05	7,45±0,02	7,34±0,01	7,35±0,05	7,38±0,07	7,38±0,06	1,00
Glu	100±20	90±10	89±20	90±16	110±30	90±18	120±22	100±27	90±15	100±12	0,38
Lactate	0,6±0,2	0,9±0,3	0,6±0,2	0,9±0,1	1,2±0,2	1,0±0,1	1,0±0,1	1,5±0,2	0,9±0,3	1,2±0,2	0,58
$HC0^3$	26,0±3,0	25±3,2	26±3,6	25±4,0	32±2,0	28±3,6	33±3,8	31±3,5	26±2,8	21±3,1	0,70
EB	2,0 ± 1,0	3,0±1,2	5,0±1,4	7,0±1,1	7,0±2,3	6,0±3,1	8,0±1,6	7,0±2,1	3,0±1,1	5,0±1,0	0,47

*ANOVA test

Source: Clinical Histories of the HUC Statistics Department

Table 8. Comparison of diuresis of neurosurgical patients at the first and third hour of trans-operative, according to year and tumor location.

Year	Tumor location	Diuresis			p* value
		1st hour	3 it was time	Total	
2018	Your Supra tentorials	300	1000	1300	<0,00001
	Your infratentorial	500	500	1000	
2019	Your Supra tentorials	400	800	1200	<0,00001
	Your infratentorial	400	300	700	
2020	Your Supra tentorials	300	1000	1300	<0,00001
	Your infratentorial	500	500	1000	
2021	Your Supra tentorials	400	400	800	1,00
	Your infratentorial	300	300	600	
2022	Your Supra tentorials	250	250	500	<0,001
	Your infratentorial	200	100	300	

*Fisher's test

Source: Clinical Histories of the HUC Statistics Department

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