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Hypertonic Saline Versus Mannitol to Improve Brain Relaxation in Craniotomy:

A Case Study

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Abstract

In neurosurgical procedures, including craniotomy for tumor, neurosurgeons often require a reduction of brain swelling to optimally perform the surgery. The reduction of brain swelling is termed brain relaxation. The anesthesia professional can accomplish brain relaxation using multiple techniques. One such technique is the infusion of certain intravenous fluids to change the osmotic pressure within the cranial vault thereby reducing brain edema (Jaffe, 2014). Highly osmolar fluids such as mannitol and hypertonic saline can be infused to decrease brain edema. Currently, mannitol remains the gold standard for medical treatment of intracranial pressure in neurosurgical procedures (Marko, 2012). This review seeks to know how hypertonic saline compares to mannitol to decrease brain edema and improve surgical field conditions in adult craniotomy patients for tumor resection. Cochrane Collections Plus and MEDLINE were searched for studies comparing the use of hypertonic saline versus mannitol for brain relaxation. Both mannitol and hypertonic saline decrease brain edema in the adult craniotomy patient. This literature review suggests that hypertonic saline significantly improves brain relaxation for surgeons during craniotomy for tumor resection, while maintaining stable hemodynamics.

The diagnosis of a brain tumor is a life-altering event, not only for the individual but also for the entire family. Meningiomas make up 34% of all primary brain tumors, and are most frequently seen in adults over the age of 60 years old with the incidence increasing with age (American Brain Tumor Association, 2015). A meningioma is actually a tumor of the meninges, which is one of the three layers of tissue that surround the brain. This type of tumor is a slow growing tumor, which may arise from many different areas around the brain. Posterior fossa tumors account for 10% of all meningiomas, and of those 5 to 11% arise from the petroclivial region (American Brain Tumor Association, 2015; DiLuna & Bulsara, 2010). Petroclivial meningiomas are rare brain tumors accounting for only 0.15% of all intracranial tumors. Despite the rarity of this type of tumor, surgical advances have improved outcomes following resection of the tumor. According to DiLuna and Bulsara (2010), over 75% of patients return to an independent functional status at one year. This case study is presented to open discussion regarding an intervention anesthesia professionals can provide to improve the surgical field, thus aiding in optimal resection of the tumor.

A seventy-two year-old male presented for a left supine orbitozygomatic craniotomy. The patient weighed 63 kg and was 167 cm, with a BMI of 22.6. The patient had recent, increasing forgetfulness and left dull eye pain. He was found to have a left petroclivial meningioma measuring 4 x 2.6 x 4.8 cm. Other past medical history included hypertension, chronic obstructive pulmonary disease, and cigarette use. The only past surgical history included a prostatectomy. He was taking lisinopril, acetaminophen, pantoprazole, atorvastatin, and cromolyn medications at home. The patient was also started on dexamethasone and levetiracetam prior to his arrival on the day of surgery. Preoperative laboratory work included a sodium level of 144mmol/L.

On the day of surgery, a pre-anesthesia evaluation was performed. The patient was awake and alert. Because the patient's primary language was not English, his orientation was difficult to assess. The patient had strong and equal strength in all four extremities. Following acquisition of appropriate consent for general anesthesia with endotracheal intubation, the patient was taken to the operating room. Once in the operating room, standard non-invasive monitors were applied, and oxygen was administered at 10 L/min via mask. After 5 minutes of pre-oxygenation, the patient was induced with intravenous Fentanyl 250mcg, Lidocaine 100mg, Propofol 250mg, and Rocuronium 50mg. A size 8 endotracheal tube was then placed using a Macintosh 3 blade for direct laryngoscopy. Bilateral breath sounds were auscultated and positive EtCO2 waveform on capnography was noted following placement of the endotracheal tube, which was then secured in place. The patient was easily ventilated with volume control mode of ventilation via mechanical ventilator. An arterial catheter was then placed without complication.

General anesthesia was maintained with Isoflurane 0.6% inspired concentration, with a mixture of 1 L/min of oxygen and 1 L/min of nitrous oxide. Following induction and intubation, the patient was given dexamethasone 10mg and levetiracetam 1.5gm intravenously. The operating table was turned 90 degrees, and the surgery was started. Prior to opening of the dura, as indicated by the surgeon, the patient was given 20% mannitol 30gm intravenous infusion. EtCO2 was maintained at 25 mm Hg via capnometry. Three hours after the start of surgery an arterial blood gas was obtained from the arterial line, and resulted at a pH of 7.49, pCO2 of 32, PaO2 of 104, HCO3 of 24, base excess of 2, ionized calcium of 1.08, lactate of 2.3, and Na of 130mmol/L. The surgeon had difficulty with inadequate relaxation of the brain, and an additional dose of 20% mannitol 30gm was infused intravenously. Albumin 5% 500 mL was infused intravenously in two separate doses throughout the case. The total crystalloid infusion

throughout the entire case was four liters of 0.9% normal saline. A repeat arterial blood gas revealed a pH of 7.47, pCO2 of 32, PaO2 of 147, HCO3 of 23, base excess of 0, ionized calcium of 1.01, lactate of 2.8, and Na of 130mmol/L. Due to a continued lack of brain relaxation and the decreased level of sodium at that time, a discussion was had between the anesthesia care team and the surgeon. The decision was made to initiate hypertonic saline therapy. An infusion of 2% saline was given with a 250 mL IV bolus followed by an infusion. The patient received a total of 500mL of 2% saline during the case. The patient also received calcium gluconate 3gm IV and Lasix 10mg IV. An arterial blood gas was obtained two hours after initiation of those treatments; showing a pH of 7.51, pCO2 of 27, PaO2 of 183, HCO3 of 21, base excess of 0, ionized calcium of 1.12, lactate of 3.3, and Na of 134mmol/L. An additional dose of levetiracetam 1gm IV and dexamethasone 10mg IV was also administered at this time. Following these treatments, the surgeon was able to successfully complete the operation.

Postoperatively, the patient remained stable with vital signs in the intensive care unit recorded as blood pressure 122/61 mm Hg, heart rate of 69 beats per minute, temperature 37 degrees Celsius, and SpO2 96%. The patient's postoperative course did include the complication of speech difficulties, but the patient was discharged home six days after the surgery.

A strong understanding of the anatomy and physiology of the brain and associated structures is important when providing anesthesia to the neurosurgical patient. Anesthesia professionals must understand the components of the blood-brain barrier, cerebral metabolism, and cerebral blood flow in order to properly deliver anesthesia during these specialized cases. The blood-brain barrier is an exclusive characteristic of the blood vessels in the brain. The cerebral blood vessels are made up of endothelial cells, which are nearly fused together. The tight junction of the cells creates a type of lipid barrier. The blood-brain barrier restricts the flow

to lipid-soluble substances only, although water may still move freely across (Butterworth, Mackey, Wasnick, 2013). An understanding of this concept is critical in understanding the way that mannitol and hypertonic saline work to decrease brain edema. According to Butterworth et al. (2013), "The movement of a given substance across the blood-brain barrier is governed simultaneously by its size, charge, lipid solubility, and degree of protein binding in blood." The large molecules of mannitol are unable to cross the blood-brain barrier, and sodium ions are restricted in their passage. When large amounts of either mannitol or hypertonic saline enter the blood, stream these substances are unable to cross the blood-brain barrier in the cerebral vasculature. This creates a hypertonicity of the plasma in the vasculature of the brain. The hypertonicity results in a transient osmotic gradient, which results in the movement of water out of the brain parenchyma into the vessels (Butterworth et al, 2013). The water can then be moved out of the cranial vault and redistributed and excreted from the body.

In order to provide appropriate neuroprotection during neurosurgical cases the anesthesia professional must understand the normal cerebral metabolism and cerebral blood flow, as well as the pathophysiology that accompanies anesthesia. Cerebral metabolism is usually expressed as the rate of oxygen consumption by the brain. Any activity or stimulation of neuronal tissue will increase the consumption of oxygen, thereby accelerating the cerebral metabolic rate. In fact, up to 60% of the oxygen consumed by the brain is used to make adenosine triphosphate (ATP) to support neuronal activity (Butterworth et al., 2013).   Nerve activity in the brain is reliant on oxygen and glucose. There is a tight relationship between the two, in order to maintain appropriate function of brain activities. When hypoxia ensues there is a lack of oxygen stores in the brain. The lack of reserve, coupled with the high rate of oxygen consumption by the brain, quickly lead to unconsciousness and cell death. The brain can also metabolize ketone bodies and

lactate in the absence of glucose. Despite this fact, hypo- or hyperglycemia may result in injury to cerebral tissue. Cerebral metabolism is closely related to cerebral blood flow. This is termed flow-metabolism coupling (Barash, Cullen, Stoelting et al., 2013). When there is an increase in the consumption of oxygen by cerebral tissue, there is a reaction to increase blood flow to the brain. Conversely, when there is a decrease in cerebral metabolic rate of oxygen consumption, there is a change in the blood flow to the brain. Cerebral blood flow is not uniform throughout the entire brain. As different areas require increased oxygen for function, vessels in the brain distribute blood flow to those areas that require it more. Stimulation and hyperthermia will elevate cerebral metabolism and blood flow. Conversely, sedation and hypothermia decrease both the blood flow as well as the cerebral metabolism (Barash et al., 2013). Factors that affect cerebral blood flow independently from cerebral metabolism include the arterial tension of carbon dioxide (PaCO2). Cerebral blood flow has a direct relationship with PaCO2. The flow increases by approximately 3% for every increase in 1mm Hg of PaCO2 (Barash et al., 2013). Contrary to the direct relationship between PaCO2 and cerebral blood flow, oxygen generally only affects blood flow at hypoxic levels. When the arterial oxygen tension (PaO2) drops below 50mm Hg, the cerebral blood flow will increase dramatically. Neuronal tissue has high demands in order to function appropriately, and a frail reserve in the absence of those requirements.

Cerebral blood flow is constant over a wide range of systemic blood pressures. This maintenance of cerebral blood flow is termed "the auto-regulation plateau" (Barash et al., 2013). Cerebral blood flow is difficult to measure both directly and indirectly, clinically. Cerebral blood flow can be conceptualized as the cerebral perfusion pressure. The cerebral perfusion pressure is the difference between the mean arterial pressure and the intracranial pressure. The Monroe-Kellie doctrine states that the cranial vault is a fixed volume. Thus, with the change of

one component, brain parenchyma, blood, or cerebral spinal fluid will necessitate a change in the volume of the other components. If there is a rise in the intracranial pressure, there must be a rise in the mean arterial pressure to maintain cerebral perfusion pressure. The cerebral perfusion pressure remains constant over a range of mean arterial pressures of 60 to 150mm Hg (Barash et al., 2013). Once these endpoints are reached, cerebral perfusion pressure is directly related to the cerebral blood flow and mean arterial blood pressure. The exact mechanism that governs the auto-regulation of cerebral blood flow is not well understood.

Anesthesia greatly affects the cerebral metabolism and cerebral blood flow. Often, the anesthesia professional will utilize or combat these effects to optimize the patient during the surgery. All inhalational agents produce a dose-dependent decrease in the cerebral metabolism. According to Butterworth et al. (2013), isoflurane produces the greatest reduction of cerebral metabolism. Isoflurane remains the agent of choice for most neuroanesthetists due to this fact. The flow-metabolism coupling, as described by Barash et al. (2013), remains intact during inhalational anesthesia. This causes little change in the cerebral blood flow at low doses of volatile anesthetic. At high doses inhalational agents cause a vasodilatory effect in the cerebral vasculature, which increases blood flow. An increase in blood flow with minimum alveolar concentration of volatile anesthetics may cause an increase in intracranial pressure (Butterworth et al., 2013). Nearly all intravenous agents have little effect on cerebral metabolism and blood flow. Ketamine is the only intravenous agent that increases cerebral blood flow and intracranial pressure due to its sympathomimetic properties (Barash et al., 2013). Propofol remains the induction agent of choice in neurosurgical procedures. Propofol decreases cerebral blood volume by decreasing cerebral blood flow and cerebral metabolism. This intravenous agent also

has anticonvulsant properties and a short half-life, which makes it optimal for assessing neuro-function at the finish of the procedure.

Barash et al. (2013) state that "the fundamental anesthetic considerations in [craniotomy] for tumor surgery are proper positioning of the patient to facilitate the surgical approach, [and] providing adequate relaxation of the brain to optimize surgical conditions." The anesthesia professional has many tools and techniques to provide the proper brain relaxation to optimize the surgical field. Dependent upon the required surgical approach, patients may be in supine, lateral, prone, or sitting positions. In the case study presented, the patient was placed in the supine position. In this position a head-up tilt with minimal extension or rotation of the neck is preferred to minimize any venous congestion that may develop in the brain (Barash et al., 2013).

Other techniques to optimize brain relaxation during craniotomy for tumor include maintenance of $PaCO_2$, temperature, and fluid balance both intra-cranially and systemically. Due to the direct correlation between $PaCO_2$ and cerebral blood flow as mentioned earlier in this paper, maintenance of $EtCO_2$ should be between 20-30mm Hg. The effects of decreasing the $EtCO_2$ to decrease cerebral blood volume are nearly instantaneous. Care should be taken not to decrease $PaCO_2$ below 20mm Hg and in instances of traumatic brain injury. Marked hypocarbia may result in cerebral ischemia secondary to an extreme decrease in cerebral blood flow. Controversy surrounds the use of hyperventilation to decrease brain edema, as it is unclear how long the effects can last. Although research has shown equilibration can occur between minutes to hours, clinically the effects of hyperventilation appear to be sustained throughout the neurosurgical procedure (Barash et al., 2013). Hypothermia causes a decrease in both cerebral metabolism as well as cerebral blood flow. Although research is clear for the use of hypothermia in the setting of cardiac arrest, it is less defined for its use as a neuro-protectant in the setting of

neurosurgical procedures. Nevertheless, research is clear that hyperthermia is detrimental in the neurological patient. Prudency in the neurosurgical patient is to maintain the patient's core temperature at 36 degrees Celsius. Steroids are also helpful in minimizing tumor edema and pressure (Barash et al., 2013). Finally, the use of hyperosmolar intravenous fluids, as well as loop diuretics, helps to minimize brain edema and maintain systemic fluid balance. The appropriate use of these fluids will be more closely examined throughout this paper.

In neurosurgical procedures, including craniotomy for tumor, neurosurgeons often require a reduction of brain swelling to optimally perform the surgery. The reduction of brain swelling is termed brain relaxation. The anesthesia professional can accomplish brain relaxation using multiple techniques. One such technique is the infusion of certain intravenous fluids to change the osmotic pressure between the brain parenchyma and vasculature thereby reducing brain edema (Jaffe, 2014). Highly osmolar fluids such as mannitol and hypertonic saline can be infused to accomplish this change and decrease brain edema.

A literature review was performed to compare hypertonic saline versus mannitol in the ability to decrease brain edema and improve the surgical field during neurosurgical procedures. The two databases Cochrane Collection Plus and MEDLINE were searched using keywords hypertonic saline, mannitol, brain relaxation, and craniotomy. Eight studies were found to be relevant to the review. One study was an animal study, and the rest were human studies or systematic reviews including human studies only. In the randomized clinical animal study, Santacruz et al. (2016) studied the use of hypertonic saline 7.45% versus mannitol 20% to decrease intracranial hypertension in a small sample of pigs. The sample size was fourteen pigs, with an additional two animals as control group. This control group, or sham surgery, received all interventions except the artificially created increase in intracranial pressure. First, the pigs

were uniformly anesthetized and monitoring intravascular lines were placed. An intra-

parenchymal balloon was placed into the brain in order to artificially raise the intracranial

pressure. The study measured the effects at two different intracranial pressures, 15 and 30 mm

Hg. At an intracranial pressure of 30mm Hg, the animals received one of the two study

solutions. Measurements were taken at the different intracranial pressures, as well as, different

time points. These authors found that at 180 minutes there was a small difference between the

groups, wherein the hypertonic saline maintained a lower intracranial pressure as well as higher

cerebral perfusion pressure. Although Santacruz et al. (2016) admit that these differences were

not statistically significant, when viewing them along with the systematic variables. There are

two large limitations to this study. This is a small animal trial that did not evaluate intracranial

pressure effects of the two groups past 180 minutes.

Due to the limited number of studies, papers researching hypertonic saline versus

mannitol to reduce intracranial pressure in the setting of other neurosurgical procedures and

conditions were also included in this review. Wakai, McCabe, Roberts, and Schierhout (2013)

provided a systematic review in the use of mannitol for acute traumatic brain injury. Kamel,

Navi, Nakagawa, Hemphill III, and Ko (2011) performed a meta-analysis comparing these two

hyperosmolar medications in the setting of elevated intracranial pressure. Finally authors Li, M.,

Chen, Chen, Cai, and Hu (2015) produced a meta-analysis reviewing mannitol versus hypertonic

saline to reduce elevated intracranial pressure in the setting of acute traumatic brain injury.

Wakai et al. (2013) performed an extensive search for randomized controlled trials of the

use of mannitol to treat patients with acute traumatic brain injury. These patients were noted to

be of a variety of severity. Only four studies were found to be inclusive of their selection

criteria. This systematic review was limited in scope to the literature review presented. Firstly,

it only examined studies where mannitol was the treatment group. Only one of the three studies compared mannitol to hypertonic saline. The other randomized controlled trials studied mannitol versus placebo, different dosages, or other medications. Wakai et al. (2013) argued that the study by Vialet (2003) suggested than mannitol may have a detrimental effect on mortality in patients with severe head injury as compared to hypertonic saline therapy. Although, Wakai et al. (2013) admits that the included study (Vialet, 2003) was only single-blinded, too small of a sample size, and did not evaluate the effects of the osmotic agent on neurological recovery.

Although Wakai et al. (2013) found insufficient evidence to make any recommendations regarding the use of mannitol in acute traumatic brain injuries; other studies have evaluated the benefits of hyperosmolar therapy in this population. Kamel et al. (2011) and Li, M. et al. (2015) included 281 patients over 12 studies to examine the effects of either hypertonic saline or mannitol on already elevated intracranial pressure. Kamel et al. (2011) performed a meta-analysis evaluating randomized clinical trials that compared hypertonic saline and mannitol in the treatment of elevated intracranial pressure. These authors included any human subject receiving equal osmolar doses of hypertonic saline or mannitol in the setting of elevated intracranial pressure with some form of quantitative intracranial pressure monitor. None of the studies included in the meta-analysis were blinded. Kamel et al. (2011) also admit that, "all the trials were small...but several amplified their sample size by including multiple episodes of elevated ICP per patient." Finally, the meta-analysis was limited by using each individual study's definition of intracranial pressure control. This decision by study authors may have led to heterogeneity in the analysis causing a bias in the results.

The article by Li, M. et al. (2015) performed a systematic review and meta-analysis to evaluate equiosmolar doses of hypertonic saline and mannitol in the treatment of elevated

intracranial pressure after traumatic brain injury. The primary outcome measured by Li, M. et al. (2015) in all studies was the mean change of intracranial pressure from baseline to the last measurement after termination of treatment. The authors posit the limitations of their study as small sample sizes, varied dosages and concentrations of study medications, and causes of brain injury other than trauma. Finally, the meta-analysis only evaluated the change in intracranial pressure over time. The article did not evaluate neurological outcomes comparison between the two treatments. Both of the above mentioned meta-analyses of randomized clinical trials found hypertonic saline to decrease elevated intracranial pressure over mannitol.

Harutjunyan et al. (2005) is a randomized clinical trial to evaluate hypertonic saline and hydroxyethyl starch versus mannitol in the treatment of elevated intracranial pressure. The study evaluated forty neurosurgical patients who were at risk for increased intracranial pressure. Of the 40 study participants, seventeen patients received the 7.2% hypertonic saline hydroxyethyl starch 200/0.5 and fifteen patients received 15% mannitol. Eight patients in the study did not have intracranial pressures greater than twenty, thus did not receive any treatment. The cerebral perfusion pressure in the hypertonic saline group was statistically higher over the mannitol group following infusion. This randomized clinical trial also evaluated a secondary outcome of whether there were any statistically significant changes in blood chemistry following infusion of either therapy. The study found no significant difference in electrolytes and plasma osmolarity between the two therapies. Although the authors did study neurosurgical patients, these patients were intensive care patients with severe neuronal damage. The study evaluated patients with elevated intracranial pressure, but excluded patients with space-occupying lesions requiring surgical intervention. Harutjunyan et al. (2005) concluded that hypertonic saline significantly decreased intracranial pressure over mannitol in their study population.

Three research studies were found to evaluate the difference between hypertonic saline and mannitol in the use of brain relaxation for neurosurgical procedures. Vilas Boas, Marques, and Alves (2011) included 29 patients for elective neurosurgery. Neurosurgical procedures included elective craniotomy, cerebral aneurysm clipping, arteriovenous malformation repairs, and cerebral tumor resections. General anesthesia was uniform across all participants provided as total intravenous anesthesia with propofol and remifentanil infusions. In the study "cerebral relaxation was evaluated by the same surgeon who was blind to the hyperosmolar therapy" (Vilas Boas et al., 2011). These authors used equiosmolar infusions of either hypertonic isoncotic saline or mannitol 20%. Vilas Boas et al. (2011) found no significant difference in the degree of brain relaxation between the two groups. Although, neurosurgeons did not consider any patient in the study to be inadequately relaxed, indicating adequacy of both treatments to provide adequate brain relaxation.

Li, J., Wang, Wang, and Mu (2014) authored a prospective randomized clinical trial to evaluate the effects of hypertonic saline-hydroxyethyl starch versus mannitol on dural tension and hemodynamics in patients undergoing elective supratentorial procedures. The authors evaluated hypertonic saline 7.2% with hydroxyethyl starch 6% against mannitol 20%. Forty patients undergoing elective supratentorial procedures including resection of gliomas, meningiomas, or other brain tumors were included in the study. General anesthesia was uniform among the entire study population. In the clinical trial, approximately thirty minutes prior to opening of the skull patients received one of two study infusions at a rate of 750mL/hour. A dural tension score was provided by neurosurgeons. Li, J. et al. (2014) found a statistically significant decrease in dural tension in the hypertonic saline-hydroxyethyl starch group versus the mannitol group. They concluded that this effect was prolonged compared to the mannitol

group. The authors measured mean arterial pressure, heart rate, cardiac index, stroke volume variation, and urine output and found that the hypertonic saline-hydroxyethyl starch group maintained a more stable hemodynamic profile as compared to the mannitol group as well. Li, J. et al. (2014) measured serum osmolality in their study as well, and found the maximum to be 330mosm/kg in the hypertonic saline-hydroxyethyl starch group. This number was well within the current guidelines of maintaining serum osmolality less than 360mosm/kg when using hypertonic saline infusions.

Prabhaker, Singh, Anand, and Kalaivani (2014) present the most up-to-date and comprehensive meta-analysis to evaluate mannitol versus hypertonic saline for brain relaxation in craniotomy patients. This systematic review included 527 patients over 6 randomized clinical trials. The studies included any adult or pediatric patient of either gender undergoing craniotomy for brain tumor who received either mannitol or hypertonic saline. The primary outcomes of this analysis were seeking to find long term outcomes and adverse events following the two treatment modalities. Unfortunately for Prabhaker et al. (2014), no studies could be found to report the long term outcomes after either treatment, or fulfill any of the paper's primary outcomes. Ultimately, only three of the trials, enrolling 387 patients, reported the outcome of brain relaxation following either treatment. In fact, in this meta-analysis brain relaxation was only viewed on a secondary outcome basis. Prabhaker et al. (2014) report that hypertonic saline is beneficial in producing more effective brain relaxation over mannitol. Although, the authors do admit that this analysis is concluded from a very limited number of studies. The authors construe that no heterogeneity was noted among the studies as well. In order to minimize any bias, two different authors independently reviewed studies for inclusion, exclusion and assessment of risk of bias.

All the studies reviewed found hypertonic saline to be at least equal to mannitol in producing brain relaxation or decreasing intracranial pressure. In fact, Harutjunyan et al. (2005), Kamel et al. (2011), Li, J. et al. (2014), Prabhaker et al. (2014), and Li, M. et al. (2015) all provided evidence that hypertonic saline produces a statistically significant decrease in intracranial pressure over mannitol. The studies in this literature review also suggest that hypertonic saline may produce a decrease in intracranial pressure, while maintaining a more stable hemodynamic state over mannitol. Hypertonic saline provides the volume expansion with less diuresis as compared to mannitol (Li, J. et al., 2014). The lack of the diuretic effects may contribute to the hemodynamic stability seen after hypertonic saline infusion.

There may be significant limitations to implementation of the results of this literature review into clinical practice. There are limited studies evaluating the outcome of brain relaxation following hypertonic saline or mannitol. Currently, all studies reviewed by this author were of limited sample size as well. Mannitol is available as 20% and 25% solutions. It is infused at doses ranging from 0.25 to 1gm/kg. Hypertonic saline is available in multiple concentrations including 2%, 3%, 5%, 7.5%, and 23% (Prabhaker et al., 2014). Hypertonic saline has the theoretical risk of causing endothelial damage at the catheter insertion site in peripheral veins, especially in the setting of extravasation (Johnson & Criddle, 2004). Most institution will not infuse hypertonic saline in concentrations above 3% without central vascular access. Risks versus benefits of placing central vascular access must be evaluated should higher concentrations of hypertonic saline be considered to enhance brain relaxation. Hypertonic saline can be administered as an intravenous bolus or infusion. Limited study sample sizes and variable dosage of hypertonic saline are the two major factors that provide limitations to this literature review.

In order to overcome these limitations, there is ample room for future research. Evidence regarding optimal concentration of hypertonic saline must be obtained. Li, M. et al. (2015) and Vilas Boas et al. (2011) were the only two studies in this review to evaluate equiosmolar doses of hypertonic saline and mannitol. Standardization of osmolarity for evaluation of hypertonic saline versus mannitol must be achieved in order to adequately evaluate clinical trials. Studies must be adequately powered. Large, multi-center randomized clinical trials are recommended in order to increase the evidence for or against the recommendation to make hypertonic saline the "gold standard" for decreasing intracranial pressure in the setting of all neurosurgical procedures.

Using the case study above assists the anesthesia professional to correlate evidence with practice. No premedication was used on this patient. As discussed above, PaCO2 has a direct correlation with cerebral blood flow. Any type of premedication may cause respiratory depression, which would lead to increased intracranial pressure as a result of the hypercarbia. The induction of anesthesia and intubation of the trachea occurred without incident. An adequate dose of opioid, in conjunction with propofol, was used to blunt the sympathetic response and provide an adequate depth of anesthesia to prevent any hypertension during tracheal intubation. Butterworth et al. (2013) describes how hypertension leads to an increase in cerebral blood volume, which increases intracranial pressure. This increase in pressure could be detrimental in patients with decrease cranial compliance due to an existing tumor. The patient's head was positioned in order to provide surgical access, while still minimizing any type of venous congestion.

Many lessons can be learned from the case study presented above. Interventions as previously discussed were implemented to provide neuroprotection, as well as optimize brain relaxation. The patient was given intravenous dexamethasone to decrease tumor edema. The

patient was maintained euthermic throughout the case. Preventing any type of hyperthermia was one factor in maintaining optimal neuroprotection (Barash et al., 2013). Isoflurane and nitrous oxide inhalational agents were used to maintain adequate depth of anesthesia during the maintenance phase of the case. The patient was maintained on mechanical ventilation with tidal volumes at approximately 6mL/kg. High mean airway pressure, as a result of large tidal volumes, could lead to increased intracranial pressure by increasing central venous pressure in the thoracic cavity (Butterworth et al., 2013). PaCO2 was maintained at 25-35mm Hg with these ventilation strategies as well. This strategy limited the increase in cerebral blood flow in correlation with the low PaCO2 to aid in brain relaxation.

Multiple considerations can be made when reviewing the literature against the timeline of the case study presented. First, a tight control of blood glucose is important to provide adequate neuroprotection. The brain relies heavily on a constant supply of glucose to perform neuronal activity. Yet, as discussed earlier, hyperglycemia can lead to ischemia. It is understood as described by Butterworth et al. (2013) that, "hyperglycemia is common in neurosurgical patients (corticosteroid effect) and has been implicated in increasing ischemic brain injury." Blood glucose was not assessed regularly throughout this case. Barash et al. (2013) suggest maintaining a range of glycemic control of 140 to 180mg/dl. While reviewing the literature the majority of studies advocate for the use of hypertonic saline to optimize brain relaxation.

In the case study hyponatremia was identified by arterial blood gas. The surgeon repeatedly stated difficulty with inadequate brain relaxation, despite the anesthesia professionals continued interventions. This author proposes in light of the evidence that hypertonic saline initiated at the start of the case may have improved surgical conditions earlier, which would have decrease the interventions provided. Notwithstanding the lack of evidence in the use of either

hypertonic saline or mannitol to improve long-term neurological outcomes, there is certainly

evidence that the use of hypertonic saline may improve brain relaxation. All medications have

consequences.

The patient in the case study required increased crystalloid, colloid, and vasopressor

administration for decreasing mean arterial blood pressure intra-operatively. The decrease of the

mean arterial pressure may lead to a decrease in cerebral perfusion pressure. Li, J. et al. (2014)

found that patients who received hypertonic saline-hydroxyethyl starch actually had an increase

in their mean arterial pressure. These authors refer to related studies, which show that an

infusion of hypertonic saline could quadruple intravascular volume. Even after four hours

following a bolus dose the plasma volume remains increased by 750mL for every one liter of

hypertonic saline administered. Li, J. et al. (2014) found a decrease in the diuretic effect of

hypertonic saline infusions, which would avoid hypovolemia and hypotension in the

neurosurgical patient. The patient in the case study may have avoided excess crystalloid and

colloid fluid administration had hypertonic saline therapy been initiated earlier in the case. The

patient could have avoided a possible decrease in their cerebral perfusion pressure due to

hypotension. Patients with cerebral perfusion pressures below 50mm Hg show changes in their

EEG, progressing with depreciating cerebral perfusion pressure ultimately to irreversible

neuronal death (Butterworth et al., 2013).

In the presented case, could the surgical time have been shortened or resection improved

with the use of hypertonic saline at the start of the case in place of the mannitol? The evidence

suggests that this may be the case. Despite the delay in recognizing the need for hypertonic

saline therapy, it was finally initiated. Vilas Boas et al. (2011) recommend serum sodium should

not be increased greater than 20mEq per day. The case study saw an increase similar to their

study. Vilas Boas et al. (2011) saw a mean increase in serum sodium of 4.56mEq thirty minutes after administration of hypertonic isoncotic saline therapy. These authors also note that an acute increase up to 160mEq serum sodium have been tolerated without harm in patients. The patient was discharged home with minor neurological deficits. As anesthesia professional encountering an aging population globally, neurosurgical procedures will continue to occur. The highest level of evidence-based practice must be implemented in order to optimize patient outcomes following neurosurgical procedures.

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