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Traumatic brain injury: a review of pathophysiology and management

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Abstract

Objective – To review current information regarding the pathophysiology associated with traumatic brain injury (TBI), and to outline appropriate patient assessment, diagnostic, and therapeutic options.
Etiology – TBI in veterinary patients can occur subsequent to trauma induced by motor vehicle accidents, falls, and crush injuries. Primary brain injury occurs at the time of initial impact as a result of direct mechanical damage. Secondary brain injury occurs in the minutes to days following the trauma as a result of systemic extracranial events and intracranial changes.
Diagnosis – The initial diagnosis is often made based on history and physical examination. Assessment should focus on the cardiovascular and respiratory systems followed by a complete neurologic examination. Advanced imaging may be indicated in a patient that fails to respond to appropriate medical therapy.
Therapy – Primary brain injury is beyond the control of the veterinarian. Therefore, treatment should focus on minimizing the incidence or impact of secondary brain injury. Because of a lack of prospective or retrospective clinical data, treatment recommendations for veterinary TBI patients are primarily based on human and experimental studies and personal experience. Therapeutic guidelines have been developed that center on maintaining adequate cerebral perfusion.
Prognosis – Severe head trauma is associated with high mortality in humans and animals. However, dogs and cats have a remarkable ability to compensate for loss of cerebral tissue. It is therefore important not to reach hasty prognostic conclusions based on initial appearance. Many pets go on to have a functional outcome and recover from injury.

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Introduction

Traumatic brain injury (TBI) in veterinary patients can occur from many types of trauma including motor vehicle accidents, falls, crush injuries, missile injuries, attacks from other animals, and inadvertent or purposeful attacks from humans.[1–5] In a recent study of brain injury, most dogs were examined following blunt vehicular trauma, while most cats were examined because of a crush injury.[3] Severe brain injury is associated with a high level of mortality in both humans and animals.[1,6] Guidelines for TBI treatment in humans have been developed and center on maintaining adequate cerebral perfusion. Appropriate therapy is controversial in veterinary medicine; however, due to a lack of retrospective or prospective clinical data most clinical recommendations are based on experimental investigations, human head trauma studies, or personal experience.[1] The following discussion will review the pathophysiology associated with TBI, appropriate patient assessment, standard treatment interventions, and innovative therapeutic strategies.

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Pathophysiology

The underlying injuries resulting from head trauma can be separated into primary injury and secondary injury categories. Primary injury occurs immediately as result of the direct mechanical damage at the time of the traumatic incident. Secondary injury occurs during the minutes to days following the trauma and is caused by

a combination of systemic extracranial insults and intracranial physical and biochemical changes.[2,4,7]

Primary brain injury involves the physical disruption of intracranial structures. Such injury includes direct damage to brain parenchyma such as contusions, hematomas, lacerations, and diffuse axonal injury. Direct vascular damage also occurs leading to intracranial hemorrhage and vasogenic edema.[1] Laceration is the most severe form of primary brain injury. Axial hematomas within the brain parenchyma and extra-axial hematomas in the subarachnoid, subdural, and epidural spaces may occur leading to compression of the brain and severe neurologic dysfunction.[8] Historically it has been believed that extraaxial hemorrhage is rare in dogs and cats suffering from TBI. However, more recent evidence suggests that this type of hemorrhage occurs in up to 10% of animals with mild head injury and in $>80\%$ with severe injury.[8–10] Direct parenchymal damage associated with primary brain injury is beyond the control of the clinician. Therefore, clinical focus should be on the prevention, recognition and treatment of secondary brain injury.

TBI leads to the activation of numerous interrelated biochemical pathways that act in concert to perpetuate further brain tissue damage. Secondary intracranial injury is largely mediated through enhanced activity of excitatory neurotransmitters, generation of reactive oxygen species (ROS), and production of proinflammatory cytokines, all of which can contribute to neuronal cell damage and possibly cell death. Cerebral edema formation, increased intracranial pressure (ICP), compromise to the blood-brain barrier (BBB) and alterations in cerebrovascular reactivity may ensue following secondary damage to neuronal tissue.[1,4,7,11]

Immediately following head injury, there is a massive release of excitatory neurotransmitters resulting in excessive metabolic activity and ATP depletion. Energy failure causes a disruption of ion homeostasis and an uncontrolled influx of sodium and calcium into neurons. Cellular (cytotoxic) edema and further cell depolarization occur. Depolarization leads to further release of excitatory neurotransmitters (such as glutamate). Glutamate mediates additional increases in intracellular calcium. Accumulation of calcium within the cells activates numerous intracellular enzymes causing severe intracellular damage and ultimately cell death.[1,2,7,12]

Several factors trigger the production of ROS after TBI, including local tissue acidosis and hypoperfusion. ROS are preferentially damaging to cell membranes containing high levels of polyunsaturated fats and cholesterol. Because brain tissue is lipid-rich it is particularly sensitive to oxidative injury.[13] In addition, hemorrhage may serve as an iron source, which favors the production of hydroxyl radicals via the Haber-Weiss reaction of the xanthine oxidase pathway.[14] Oxidative damage is thought to play a major role in secondary brain injury.[1,7,13,15]

TBI is associated with the release of inflammatory cytokines followed by the infiltration and accumulation of inflammatory cells.[16] These inflammatory mediators perpetuate secondary brain injury by activating the arachidonic acid and coagulation cascades, disrupting the BBB, and inducing nitric oxide (NO) production. NO is thought to lead to excessive vasodilation leading to the loss of pressure autoregulation. In addition, NO contributes to ROS- and glutamate-mediated tissue damage.[4,7,12]

ICP is a common and potentially deadly sequel to TBI. The Monroe-Kellie doctrine holds that the skull is a rigid compartment that contains 3 components: brain parenchyma, arterial and venous blood, and CSF. Under normal circumstances, these components exist in a state of balanced dynamic equilibrium. If an increase occurs in the volume of one component, such as brain tissue, the volume of one or more of the other components must decrease or an elevation in ICP will result. This accommodation is known as intracranial compliance and accomplished by fluid shifts in the brain vasculature and CSF pathways. Sudden increases in any of these compartments, as occurs in primary or secondary brain injuries, must lead to a decrease in one of the other components or an increased ICP will result. Intracranial compliance has limitations and decreases as ICP increases. If ICP increases beyond the limits of the compensatory mechanisms cerebral perfusion is compromised and ischemia of brain tissue occurs.[1,2,11,12,17–19] Severe increases in ICP trigger the cerebral ischemic response, or Cushing reflex. Increases in ICP result in decreased cerebral blood flow (CBF), which leads to increased CO_2 that is locally sensed at the vasomotor center. The vasomotor center initiates a sympathetic nervous system response leading to an elevated mean arterial pressure (MAP) in an attempt to increase cerebral perfusion pressure (CPP). The systemic hypertension is detected by baroreceptors, located in the walls of the carotid arteries and aortic arch, resulting in a reflex bradycardia. The ischemic response occurs late, indicating possible life-threatening elevation in ICP, and should prompt the clinician to initiate aggressive treatment.[20]

Systemic contributions to secondary brain injury include hypotension, hypoxia, hypo- or hyperglycemia, hypo- or hypercapnia, and hyperthermia.[1,4,7] These extracranial events may result in worsening of cerebral injury as a result of compromised cerebral perfusion. CPP is the force driving blood into the calvarium and providing essential oxygen and nutrients to the

parenchyma, and is the primary determinant of CBF. CPP is defined as the difference between MAP and ICP. Via autoregulatory mechanisms the normal brain is capable of maintaining a constant CBF over a range of MAP of 50–150 mm Hg. When there is compromise of cerebral autoregulation as occurs following TBI this pressure autoregulatory function is compromised making CBF even more dependent on CPP. In this situation even small decreases in CPP can lead to changes in CBF and result in ischemic injury to the brain parenchyma.[2,11,12,17,18,21]

Patient Assessment

Initial assessment of TBI patients focuses on imminently life-threatening abnormalities. Human studies have shown that approximately 60% of patients with TBI have concurrent injuries to other major organs.[22] As in any trauma patient, the ABCs (airway, breathing, cardiovascular status) of emergency management are critical and addressed first. Hypovolemia and hypoxemia must be recognized and treated immediately as they are strongly correlated with elevated ICP and increased mortality in human TBI victims.[1,11,23–26] Respiratory system dysfunction may be seen following TBI. Concurrent injuries seen include pneumothorax, hemothorax, rib fractures, and pulmonary contusions. A severe respiratory abnormality that may be seen is neurogenic pulmonary edema (NPE). The pathogenesis of NPE is not completely understood. It is believed that there is CNS overstimulation of sympatho-adrenal activity, causing marked peripheral vasoconstriction and increased venous return. The resulting systemic hypertension leads to markedly elevated left ventricular afterload and diminished left ventricular stroke volume. Blood then accumulates in the pulmonary circulation resulting in pulmonary capillary hypertension and subsequent edema. NPE can cause dyspnea, hypoxemia, and hypercapnia. Hypercapnia leads to cerebral vasodilation and an increased ICP. While the effects of NPE are severe, it is typically self-limiting and will resolve in a matter of hours to days.[27–29] A minimum database includes a PCV, total protein level, blood glucose, electrolyte levels, and a urine specific gravity. Specific attention is paid to the serum glucose level as hyperglycemia has been demonstrated to relate to head trauma severity in animals and in humans.[3,30–32]

Once normovolemia and appropriate oxygenation and ventilation are established, the patient is carefully examined for other traumatic injuries. These include skull and vertebral fractures, and injuries to the respiratory system and abdominal organs. A complete neurologic examination can then be performed. Specific medical therapy for TBI, as discussed below, is instituted. Additional diagnostic testing such as radiography and laboratory testing may be warranted at this time.

Neurologic Assessment

Initial neurologic assessment includes evaluation of the patient's state of consciousness, breathing pattern, pupil size and responsiveness, ocular position and movements, and skeletal motor responses. A scoring system can be used to facilitate logical treatment decisions and serial objective patient evaluations.[5,24,33]

In human patients TBI is graded as mild, moderate, or severe based on the Glasgow coma scale. A modified Glasgow coma scale (MGCS) has been proposed for use in veterinary medicine and evaluated with respect to survival over a 48-hour period.[5] This scoring system may provide an estimate of prognosis for the veterinarian and owner. The MGCS incorporates 3 categories of the examination (ie, level of consciousness, motor activity, brainstem reflexes) and assigns a score from 1 to 6, providing a total score of 3–18. Higher scores correlate with a better prognosis.[5] However, given the limited data available correlating survival with a numerical score, the MGCS may be better utilized as a objective assessment of progression of neurologic signs rather than as a prognostic indicator.

The level of consciousness is the most reliable empiric measure of impaired cerebral function after head injury providing information about the functional capabilities of the cerebral cortex and the ascending reticular activating system (RAS) in the brainstem. Decreasing levels of consciousness indicate abnormal function of the cerebral cortex or interference with transmission of sensory stimuli by the brainstem or RAS. Patients presenting in a coma generally have bilateral or global cerebral abnormalities or severe brainstem injury and have a guarded prognosis.[5,33–35] Motor activity may be affected by the animal's level of consciousness. Opisthotonus with hyperextension of all four limbs is suggestive of decerebrate rigidity, or cerebral damage. Variable flexion and extension of the hind limbs is seen with decerebellate rigidity, or cerebellar damage.[35] However, the main determination between cerebral and cerebellar injury is level of consciousness. Damage to the RAS within the midbrain, as seen in the decerebrate patient, results in a comatose state. This is associated with a grave prognosis.[5,34–36]

Neuro-ophthalmologic examination is the foundation of the brainstem reflexes category. Evaluation for concurrent ocular trauma is integral for appropriate assessment. Pupils that respond appropriately to light indicate adequate function of the rostral brainstem,

optic chiasm, optic nerves, and retinae. Miotic pupils indicate diffuse forebrain injury. Progression to mydriasis may indicate brain herniation. Transtentorial herniation places pressure on the third cranial nerve, interrupting parasympathetic input to the eye and resulting in a dilated pupil. In addition to pressure on the third cranial nerve, transtentorial herniation compresses the brainstem. Fixed, unresponsive and midrange pupils are seen with cerebellar herniation. Brain herniation is associated with severe disability and death if not treated rapidly and aggressively.[35,36] Repeated neurologic assessment is recommended every 30–60 minutes to monitor treatment efficacy and to assess for deterioration.

Medical Therapy

Once initial patient assessment has occurred, medical intervention can proceed. Initial extracranial stabilization takes place first, closely followed by therapies directed toward intracranial stabilization. Extracranial stabilization involves the correction of tissue perfusion deficits, typically as a result of hypovolemia, and optimizing systemic oxygenation and ventilation. Goals for intracranial stabilization include optimizing cerebral perfusion, decreasing ICP, and minimizing elevations in the cerebral metabolic rate.[7,23]

Initial Extracranial Therapy

Fluid therapy

The primary goal of fluid therapy in trauma is rapid restoration of intravascular volume to ensure adequate CPP. Historically, there have been recommendations to limit the volume of fluid administered to TBI victims due to the concern that aggressive IV fluid administration may exacerbate brain edema. However, there are little data to support the idea that dehydration diminishes cerebral edema and these recommendations for fluid restriction are firmly contraindicated.[1,2,11,25,26,34,37] Hypotension has been shown to be associated with significant increases in morbidity and mortality in human TBI patients. In 1 prospective study, hypotension was associated with a 150% increase in mortality.[38] As such, resuscitation protocols for brain injured patients should vigilantly avoid hypovolemia. Immediate restoration of blood volume is imperative to ensure normotension and adequate CPP.[38]

Controversy exists regarding the best type of fluid to utilize in the resuscitation of a TBI patient.[39,40–45] Options include isotonic crystalloids, hypertonic crystalloids, artificial colloids, and blood products. An intact BBB is freely permeable to water but nearly impermeable to ions and larger, colloid-sized molecules due to the tight intercellular junctions.[41,46] Studies have shown that colloid solutions exert little influence on cerebral water content and on ICP. It is the osmolality, rather than the plasma oncotic pressure, that determines water movement between the vascular and extravascular compartments.[39,41,43,46–48] As such, in the uninjured brain, there should be minimal concern that aggressive crystalloid resuscitation may produce cerebral edema formation by redistribution into the interstitial space. However, in the injured brain the BBB may be disrupted regionally or globally. This disruption may result in increased permeability to both ions and colloidal particles in a nonselective manner.[42] In this situation the choice of fluid for resuscitation could have an impact on cerebral edema formation. Regardless, the benefit obtained by the restoration of CPP with either crystalloids or colloids outweighs the potential risks. One quarter aliquots of the shock dose of isotonic crystalloids (90 mL/kg in the dog; 60 mL/kg in the cat) or artificial colloids (10–20 mL/kg) are given rapidly until improved tissue perfusion (assessed by normalization of heart rate, pulse quality, mucous membrane color, capillary refill time, and blood pressure) is achieved.[23]

Hypertonic saline is capable of resuscitating profound hypovolemic shock in small volumes and may be a superior resuscitation fluid for TBI patients.[48,49] After IV administration there is a rapid rise in osmolarity that promotes transcapillary shift of interstitial and intracellular fluid into the vasculature. The effect is a rapid and marked volume expansion that exceeds the volume infused.[48,49,50] The recommended dose for volume expansion is 4 mL/kg of 7.5% sodium chloride[51] or 5.3 mL/kg of 3% sodium chloride[52] administered over 2–5 minutes. The peak volume-expansion effect occurs within minutes of administration. Hypertonic saline is a crystalloid solution. So, although its volume-expanding effects are immediate, subsequent redistribution to other fluid compartments limits its duration of volume expansion effect to between 15 and 75 minutes.[53] The addition of an artificial colloid prolongs the effects to several hours presumably by retaining fluids in the intravascular compartments, thereby maintaining an intravascular oncotic gradient.[40,53] The coadministration of hypertonic solutions and colloids is more effective at restoring blood volume than administration of either solution alone.[54] The author recommends a dose of 4 mL/kg total of a 1:2 ratio combination of 23.4% hypertonic saline with 6% Hetastarch.

After initial fluid resuscitation continued fluid therapy is mandatory. Hypertonic solutions act to dehydrate tissues so it is essential that isotonic crystalloid solutions be administered after administration of hypertonic saline. Fluid therapy must provide maintenance requirements and account for ongoing losses.

Oxygenation and ventilation

Oxygen supplementation is recommended for most TBI patients. Decreased oxygen delivery is a main perpetrator of secondary brain insult. Human studies in TBI patients have shown that mortality for patients with documented hypoxia after injury is double that of patients without documented episodes of hypoxia.[38] Oxygenation status may be estimated using respiratory rate and pattern, mucous membrane and tongue color, and thoracic auscultation.[25] Pulse oximetry is a method of determining oxygenation status. Oxyhemoglobin saturation (SpO_2) values from pulse oximeters over 95% are considered normal and reflect a partial pressure of oxygen in arterial blood (PaO_2) of at least 80 mm Hg. An SpO_2 value below 89% (PaO_2 level <60 mm Hg) indicates a serious level of hypoxemia and a SpO_2 value below 75% (PaO_2 level <40 mm Hg) indicates a lethal level of hypoxemia.[55,56] If arterial blood gas analysis is available, the PaO_2 should be maintained at or above 90 mm Hg. Also of importance is to maximize arterial oxygen content and decreased oxygen delivery to the tissues by ensuring adequate hemoglobin levels and blood pressure.

Supplemental oxygen can be administered to conscious patients by a face-mask, nasal oxygen cannula, or a transtracheal oxygen catheter. The use of an oxygen cage is typically ineffective as these patients require frequent monitoring which does not allow for a closed system and a high oxygen environment. Nasal oxygen cannulas and transtracheal oxygen catheters supply approximately 40% inspired oxygen concentration with flow rates of 50–100 mL/kg/min. It is important that the patient tolerates the method of oxygen supplementation, however, as struggling, anxiety, and coughing may increase ICP.[1]

The most important factor controlling CBF and cerebral blood volume (CBV) in the normal brain is the partial pressure of arterial carbon dioxide ($PaCO_2$).[18] Plasma CO_2 tension regulates cerebral blood vessel diameter. Hypercapnia will lead to cerebrovascular dilation with blood flow in excess of demand. This excess blood volume will in turn lead to an increased ICP.[25,57] Arterial blood gas measurement is the most accurate method to monitor $PaCO_2$ levels. Venous carbon dioxide levels may also be used in place of arterial blood gas values. However, the venous carbon dioxide levels are typically 5 mm Hg higher than the $PaCO_2$. In intubated patients end-tidal CO_2 measurement is a useful tool but tends to underestimate the actual $PaCO_2$ level.[58] Hypoventilating patients may require intubation and mechanical ventilation.[1]

Hyperventilation has traditionally been viewed as a method of decreasing ICP. Hyperventilation decreases CO_2 tension leading directly to cerebral vasoconstriction, thereby decreasing CBV and lowering ICP.[25,57] However, it has been shown that even moderate hypocapnia (CO_2 <34 mm Hg) leads to excess vasoconstriction, reducing global CBF and perpetuating cerebral hypoperfusion in the TBI patient.[59] The hypoperfused brain tissue is at increased risk of ischemic injury. Limiting the use of hyperventilation following severe TBI may help improve recovery, or at least avoid iatrogenic cerebral ischemia. Aggressive hyperventilation may still be considered necessary for brief periods of time in patients with acute deterioration in neurologic status. However, these patients are not hyperventilated below a $PaCO_2$ of 30 mm Hg.[59–61]

Initial Intracranial Therapy

Minimizing increases in ICP

Simple therapies may be instituted to help minimize increases in ICP. Positioning the head such that it is elevated at a 15–30° angle from the horizontal functions to reduce CBV by increasing venous drainage from the brain without deleterious changes in cerebral oxygenation. A stiff board should be used to elevate the entire thorax along with the head in order to prevent bending of the neck and obstruction to venous drainage.[62] It is also important to ensure that no constrictive collars or wraps, including jugular catheters, obstruct the jugular veins as this elevates the ICP.[2]

Hyperosmotic agents

Hyperosmolar therapy is the treatment of choice for increased ICP after TBI.[63] Mannitol is the osmotic diuretic traditionally used in humans and animals.[64,65] Because of risks associated with its administration, however, new treatment modalities such as hypertonic saline are being investigated.

Mannitol is recommended in patients with evidence of severe TBI and progressive neurologic deterioration. It is considered the first-line therapy for decreasing ICP and improving CPP.[63] The recommended mannitol dose ranges from 0.5 to 1.5 g/kg as a slow bolus over 15–20 minutes.[66] One study showed that high-dose (~1.4 g/kg) therapy resulted in significant neurologic improvement compared with low-dose (~0.7 g/kg) therapy.[67] Controversy exists regarding the exact mechanisms by which mannitol exerts its effects. Administration causes a transient plasma expansion decreasing blood viscosity. This results in cerebral vascular vasoconstriction to maintain CBF. Thus, ICP decreases secondary to a decreased CBV despite maintained CBF.[68–72] This rheologic mechanism is thought to be responsible for the most profound effect on ICP and occurs immediately after administration and persists for approximately 75 minutes.[64] Osmotic effects of

mannitol are delayed for 15–30 minutes after administration. In the nontraumatized brain mannitol promotes the shift of water from the intracellular and interstitial spaces of the brain into the vasculature, inducing an osmotic diuresis, thereby reducing cerebral edema. This effect peaks 1 hour after administration and may persist for 6–8 hours. However, this mechanism of action may have limited effect in the traumatized brain due to decreased perfusion of the parenchyma.[66,68] Mannitol has also been reported to have free radical scavenging properties that may function to limit secondary oxidative injury in the brain.[73] Historically, the concurrent administration of furosemide with mannitol has been advocated. It was believed that furosemide decreased CSF production and acted synergistically with mannitol to prolong the osmotic gradient and lower the ICP.[74] However, more recent evidence has shown that while mannitol increases plasma osmolality and decreases the water content of the injured brain the addition of furosemide has no effect. Brain water in patients treated with mannitol (8 g/kg) plus furosemide (8 mg/kg) did not differ from those treated with mannitol (8 g/kg) alone.[75] Because of the lack of evidence and the risk of worsening hypovolemia the use of furosemide is no longer recommended in TBI patients.[63]

Mannitol administration is contraindicated in hypovolemic patients due to its accompanying diuretic effect that can exacerbate dehydration and volume contraction. Mannitol increases plasma volume, renal blood flow, and glomerular filtration rate. Being freely filtered, it retains fluid within the renal tubules resulting in wasting of electrolytes and water.[76] It is therefore important that mannitol is administered only to normovolemic patients and is followed with appropriate crystalloid therapy to prevent dehydration and hypotension.

A frequently raised theoretical concern with mannitol administration has been in the exacerbation of ongoing intracranial hemorrhage by its osmotic effect. However, there is no clinical evidence to prove this theory and, as the benefits of treatment far outweigh the theoretical risks, it may be disregarded.[1,2,24] Another reported drawback of mannitol therapy is the concept of reverse osmotic shift. In situations of prolonged contact (multiple bolus doses or continuous infusions) mannitol can accumulate in the extravascular compartment exceeding the intravascular concentration and leading to brain edema and an increase in ICP. However, reverse osmotic shift is less likely to occur with appropriate bolus use of mannitol.[77]

Hypertonic saline is another hyperosmotic agent being investigated for the treatment of cerebral edema and elevated ICP. The intact BBB is relatively impermeable to sodium and chloride. In hyperosmolar concentrations sodium chloride creates a driving force shifting water from the interstitial and intracellular spaces of the brain into the intravascular compartment, thus reducing brain water content and ICP. Hypertonic saline administration also improves regional CBF via dehydration of cerebrovascular endothelial cells. Reduction of endothelial edema causes a relative increase in vessel diameter improving CBF leading to a reduction in ICP and enhanced cerebral oxygen delivery.[78] Hypertonic saline solutions have also been shown to decrease brain excitotoxicity by promoting reuptake of excitatory amino acids, such as glutamate, into the intracellular space,[79] and by reducing adhesion of polymorphonuclear cells to microvasculature modulating the inflammatory response.[80] The recommended dose of hypertonic saline is controversial, with studies looking at varying strengths and administration protocols.[48,51,52,78–85] Currently recommended doses include 4 mL/kg of 7.5% sodium chloride[51] or 5.3 mL/kg of 3% sodium chloride[52] administered over 2–5 minutes. Although the volume expansion effects of hypertonic saline last approximately 15–75 minutes[53] the beneficial effects on ICP are maintained far longer.[40,52]

Hypertonic saline administered to chronically hyponatremic patients can lead to a rapid or severe elevation of sodium levels, leading to neurologic signs such as decreased mentation and seizures, or more seriously, cerebral dehydration.[86] This leads to signs of depression, weakness, and ataxia that progresses to spastic paresis with loss of postural reactions and hypermetria, episodic myoclonus, and impaired sensory perception.[87] Hyponatremia must be excluded before treatment with hypertonic saline. Because of its rapid volume expanding effects, hypertonic saline also carries a risk of aggravating pulmonary edema or contusions in patients with underlying cardiac or respiratory pathology. However, this risk exists for mannitol as well and may be worse than hypertonic saline in the patient with pulmonary contusions.[88]

Studies have been performed comparing mannitol and hypertonic saline solutions in humans and animals.[52,81,85,89] When equimolar doses of mannitol, 3% NaCl, and 23.4% NaCl were compared in a ovine model of intracerebral hemorrhage, ICP reduction was most prominent after 23.4% NaCl administration.[52] However, after 2 hours only 3% NaCl had a sustained effect on ICP and the ICP in the mannitol-treated animals exceeded the pretreatment ICP. The CPP was also higher in the 3% NaCl treated group compared with mannitol. This study suggests that hypertonic saline may actually be favored over mannitol.[52] A study using a rodent model of acute brain injury compared the efficacy of single, equimolar bolus doses of 23.4% hypertonic saline and mannitol in reducing elevated ICP.[47]

Hypertonic saline resulted in a greater absolute ICP decrease and a more sustained effect than mannitol.[47] Another study comparing the effects of equimolar doses of 20% mannitol and 7.5%saline/6% dextran-70 in human patients with increased ICP demonstrated that the hypertonic saline-dextran solution lowered ICP more effectively than mannitol. The study also demonstrated that the hypertonic saline-dextran solution had a longer duration of effect than mannitol.[81]

At this time The Brain Trauma Foundation Guidelines still consider mannitol to be the first line treatment for increased ICP in cases of TBI.[63] However, recent studies support the growing clinical literature that hypertonic saline may in fact be superior to mannitol in controlling ICP with fewer untoward effects. It may be especially valuable in situations of shock and hypotension when administered with an artificial colloid. Hypertonic saline may also be beneficial in cases that have already received multiple mannitol doses. Additional studies are needed before a firm recommendation can be made on the appropriate use and concentration of hypertonic saline in TBI.

Ancillary Therapies

Glycemic control

Studies have shown that hyperglycemia is associated with increased mortality rates or worsened neurologic outcomes in human patients with head trauma[30,31] and in animals with experimentally induced head trauma.[32] In human literature there is ongoing debate as to the degree in which hyperglycemia is a reflection of brain injury or a cause of worsened secondary injury. It has been shown that hyperglycemia following trauma is a result of a sympatho-adrenal response. Therefore, the degree of hyperglycemia may simply be a reflection of the severity of the injury sustained. However, although the exact mechanism has not yet been established, studies have also shown that hyperglycemia potentiates neurologic injury.[3,90–92] Hyperglycemia increases free radical production,[93] excitatory amino acid release,[94] cerebral edema,[95] and cerebral acidosis,[96] and alters the cerebral vasculature.[97]

A study of hyperglycemia in naturally occurring TBI in dogs and cats suggested that the degree of hyperglycemia after TBI is associated with the severity of head trauma.[3] The degree of hyperglycemia, however, was not associated with outcome of the animals in the study. Control of blood glucose concentrations with insulin was not investigated. Nonetheless, hyperglycemia has been shown to have detrimental effects in patients with TBI and so iatrogenic hyperglycemia, such as may occur with corticosteroid administration, must be prevented.[3,23]

Hypothermia

Hypothermia has been employed as a treatment strategy in human TBI patients[98–100] and recently reported in a canine patient.[101] Yet the mechanism by which hypothermia limits secondary brain injury is not well defined. Hypothermia was traditionally thought to decrease brain metabolic demands leading to decreased cerebral edema and ICP.[1] Currently, induced hypothermia is thought to provide beneficial results through reduction in the release of excitatory neurotransmitters such as glutamate.[98] Hypothermia may also reduce secondary brain injury by inhibition of the posttraumatic inflammatory response including a reduction in the release of inflammatory cytokines and preservation of the BBB.[98]

A human clinical trial demonstrated improvement in treatment time and neurologic outcome in patients with severe TBI treated for 24 hours with moderate hypothermia (32–34°C) when compared with normothermic controls.[98] Patients were cooled to 32–34°C using cooling blankets and nasogastric lavage with iced saline. Hypothermia was maintained for 24 hours after which the patients were passively rewarmed over another 12 hours.[98] Conversely, a National Acute Brain Injury Study in adult patients with TBI could not demonstrate a beneficial effect of iatrogenic hypothermia.[99] Patients were cooled by means of surface cooling with ice and gastric lavage with iced fluids and maintained at 33°C for 48 hours. Patients in the hypothermia group had more complications but no difference in mortality.[99] As the current literature has failed to consistently support the positive influence of prophylactic hypothermia on mortality and morbidity its use cannot be recommended as standard therapy for TBI patients at this time.[100]

Potential disadvantages to induced hypothermia include coagulation disorders, increased susceptibility to infections, hypotension, bradycardia, and arrhythmias. These complications typically occur with more severe hypothermia (30°C or lower).[25] At this point the question still remains as to whether hypothermia may benefit dogs and cats with TBI. However, hyperthermia, which may be due to direct trauma to the thermoregulatory center, excitement, seizure activity, pain, or iatrogenic causes ought to be avoided and necessitates immediate treatment as it increases cellular metabolism and vasodilation leading to increased ICP.

Pain Management

Adequate analgesia is critical in the prevention of further ICP elevation in TBI patients. Opioids are commonly used analgesics in critically ill patients due to their relative lack of adverse cardiovascular effects and

ease of reversal. Opioids do have adverse effects, such as respiratory depression and hypotension, which may have a greater consequence in the presence of ICP elevation. However, when titrated to achieve adequate analgesia opioids have been shown to be safe.[102] In the presence of cardiovascular shock or BBB damage opioid dose requirements may be decreased, so care is taken to avoid overdoses. The opioid agonists fentanyl and morphine can be administered as a constant rate infusion (CRI), which helps avoid peaks and troughs in analgesia and the adverse effects seen at higher blood levels.[103] Recommended CRI doses for fentanyl include 2–6 μg/kg/h and 0.1–.5 mg/kg/h for morphine.[104] Pure opioids may be reversed using naloxone, an opioid antagonist, if significant respiratory or cardiovascular depression occurs. The opioid agonist/antagonists and partial agonists such as butorphanol and buprenorphine, respectively, are often thought to be safer analgesics because they cause less cardiovascular and respiratory depression.[103–105] However, when administering the drug to a patient with TBI that is at risk for rapid changes in neurologic status, it is important to consider that the effects of buprenorphine are difficult to reverse with naloxone.[104] It is also important to keep in mind that butorphanol has a short duration of analgesia and if given IV dosing may need to be repeated every 2 hours or more frequently.[105] It may be more prudent to use a drug, such as fentanyl, that has a short half-life and is easily reversed if needed.

Anticonvulsant therapy

It has been reported that seizures complicate between 4% and 42% of cases of severe TBI in human patients.[106] Risk factors for posttraumatic seizures include severity of injury, depressed skull fractures, epidural, subdural, and intracerebral hematomas, penetrating head wounds, and a seizure within the first 24 hours following injury.[106] Studies in humans have shown that anticonvulsants administered prophylactically reduce the incidence of seizures within the first week following trauma, but do not reduce the incidence of seizures after the first week.[106] The studies have not shown that prevention of posttraumatic seizures improves outcome.[106] The role of prophylactic anticonvulsant therapy in animals following TBI remains unclear.

Adverse effects of seizure activity include hyperthermia, hypoxemia, and cerebral edema.[23] These effects exacerbate increased ICP in patients with TBI and so any seizure activity is treated aggressively. Diazepam is the anticonvulsant of choice for stopping an ongoing seizure due to its rapid onset of action and reliable efficacy.[23] For prevention of further seizures this author prefers phenobarbital as an anticonvulsant agent. An initial loading dose of 16–20 mg/kg, as a single dose or incrementally, is administered to reach steady state levels faster. After loading a dose of 2–3 mg/kg is administered twice daily.[107] As phenobarbital may cause respiratory depression, carbon dioxide levels should be monitored and hypoventilation addressed.

Barbiturates

Barbiturates have the ability to decrease the energy of cerebral tissue. Lowering the energy requirement may decrease oxygen demand by neuronal tissue resulting in vasoconstriction and decreased blood flow. This decreased blood flow may, in turn, lead to decreased ICP.[25]

The use of pentobarbital for induction of a barbiturate coma may be used to decrease metabolic demands of the brain. However, this therapy is instituted only when other therapies have failed. There is limited evidence for the efficacy for barbiturate use, and induction of a barbiturate coma may be detrimental to survival.[25] The use of a barbiturate coma has not yet been reported in the veterinary literature. Human clinical trials have shown that prophylactic barbiturate use does not prevent an increase in ICP and may worsen outcome as compared with other therapies.[108] Nevertheless, in patients with increased ICP that is refractory to other therapies, barbiturate use has improved outcome when used as a last resort.[109] Pentobarbital is the barbiturate of choice for TBI patients.[25,108,109] An initial IV bolus dose of 2–15 mg/kg is administered for induction. The dose is carefully titrated to effect using small incremental boluses over 20 minutes. A CRI at a dose of 0.2–1.0 mg/kg/h is administered to maintain the barbiturate coma.[107] Cardiovascular and respiratory depression leading to hypotension and hypoventilation are potential complications of barbiturate use. As a result, intensive monitoring and controlled mechanical ventilation are required to prevent adverse effects on cerebral perfusion.[107]

Corticosteroids

Recent clinical trials in humans have shown that the use of corticosteroids, including methylprednisolone, increases mortality in patients suffering from head trauma.[110,111] These drugs are now contraindicated in human medicine. As a result, the use of corticosteroids in head trauma patients has fallen out of favor in veterinary medicine. Corticosteroids have also been associated with hyperglycemia, immunosuppression, delayed wound healing, gastric ulceration, and the exacerbation of a catabolic state. These adverse effects, in combination with the increased mortality following

their use in humans, preclude the recommendation for corticosteroid use veterinary head trauma patients.[23]

GI protectants

A number of risk factors have been associated with stress ulceration in human trauma patients. Single-system injuries of the CNS have been found to be independently predictive of bleeding;[112] therefore, routine stress ulcer prophylaxis is recommended in these patients.[113] The cornerstone of gastric ulcer treatment and prevention is the reduction of gastric acid secretion. A reduction of gastric acidity to a pH >4 is effective in preventing stress ulceration, but a pH >6 is required to control actively bleeding ulcers.[114] Treatment options include the use of histamine-2 receptor antagonists (H_2-RAs), proton pump inhibitors (PPIs), and sucralfate.

H_2-RAs are analogs of histamine that competitively and reversibly inhibit the binding of histamine to H_2 receptors on the gastric parietal cell leading to a reduction in the secretion of acid.[115] Available H_2-RAs include famotidine, ranitidine, nizatidine, and cimetidine. A recent veterinary study established that treatment with ranitidine was no different than treatment with saline.[116] This same study showed that famotidine, administered at 0.5 mg/kg IV twice daily, was significantly more effective than saline administration in increasing the intragastric pH.[116] In addition, cimetidine and ranitidine inhibit the cytochrome P-450 system potentially interfering with drug clearance, while famotidine does not inhibit this enzyme system. As a result, famotidine is often the recommended H_2-RA and is considered to be quite safe.[115]

PPIs are converted to their active form in acidic compartments, which then covalently bind to the hydrogen ion-potassium ion ATPase enzyme, blocking its activity. Blocking this pump results in an irreversible inhibition of gastric acid secretion.[115] Inhibition of the hydrogen ion-potassium ion ATPase occurs only when the pump is present on the apical membrane of the parietal cell. These pumps are postprandially recruited to the apical membrane from intracellular vesicles. Therefore, PPIs are administered 1 hour before a meal so that peak serum concentrations coincide with maximal activity of proton pump secretion.[117] Commonly used PPIs in veterinary medicine include orally administered omeprazole and IV formulations of pantoprazole and lansoprazole. A recent veterinary study found that only omeprazole showed an improvement in gastric acid inhibition by the second day, as assessed by a gastric pH maintained ≥ 3, when compared with the H_2-RAs famotidine and ranitidine.[116] By the sixth day, however, there was no difference found between famotidine, omeprazole, or pantoprazole in the percentage of time the intragastric pH was ≥ 3 and ≥ 4 or in the median intragastric pH.[116] Human studies have reported that PPIs are more efficacious than H_2-RAs in inhibiting gastric acid secretion;[114] however, this was not found to be true in dogs.[116] Omeprazole may have an added benefit in TBI patients. Although the mechanism of action is unclear, omeprazole has been shown to decrease CSF production in dogs by 26%.[118]

Sucralfate is a sulfated disaccharide-aluminum hydroxide complex that dissociates in the stomach into its components. It forms a paste-like substance that binds to the positively charged proteins in the base of ulcers or erosions for up to 6 hours. This complex forms a barrier preventing back diffusion of hydrogen ions and inactivating pepsin thereby protecting ulcers from further damage. Sucralfate works best in an acidic environment; however, it is effective at near-neutral pHs and so can be used concurrently with the antisecretory drugs.[115]

There is no clear preferred drug choice for the reduction in gastric acidity in veterinary patients as a result of conflicting study findings. However, gastric ulcer prophylaxis is recommended due to the risk of gastrointestinal bleeding seen with TBI.[112,113]

Motility modification

Enteral feeding intolerance secondary to abdominal distension, increased gastric residuals, ileus, delayed gastric emptying, and diarrhea has been documented in human TBI patients.[119] Delayed gastric emptying may be attributable to multiple factors including increased ICP, sympathetic nervous system stimulation, cytokine release, hyperglycemia, and opioid use.[120] Delayed gastric emptying has potential serious implications for increased morbidity and mortality such as poor nutrition, bacterial colonization of the gastrointestinal tract, gastroesophageal reflux, and an increased incidence of aspiration pneumonia.[121] However, studies have also shown that intragastric enteral feeding coupled with a prokinetic agent can be safely accomplished in the majority of TBI patients.[122]

A recent human study evaluating metoclopromide showed no significant prokinetic effect on gastric emptying in TBI patients.[120] Cisapride accelerates gastric emptying, but it is not available IV and its effectiveness in patients with slow gastric emptying who may not absorb the drug enterally is unknown. Human studies have shown that low dose erythromycin (1–3 mg/kg IV) increases the rate of gastric emptying in patients who are intolerant of enteral feeding.[123] Another recent human study showed that combination therapy with erythromycin and metoclopromide is more effective than erythromycin alone in improving the success of enteral feeding.[124] This combination therapy also decreased the incidence of tachyphylaxis and was

associated with the delivery of a greater proportion of feedings with no major adverse effects.[124] A more novel therapy recently evaluated in human patients is the use of naloxone administered orally to avoid antagonism of the central effects of parenteral opiates. Oral administration of this opioid antagonist in mechanically ventilated patients receiving opioid analgesia has been found to improve the success of enteral feedings and reduce the incidence of aspiration pneumonia.[125]

Although these studies have been performed in human TBI and other critically ill patients, the information gathered can be extrapolated for use in veterinary medicine. Given the high incidence of delayed gastric emptying seen in critically ill humans it would be prudent to institute the use of promotility agents coupled with enteral feeding in veterinary TBI patients.

Nutrition

TBI results in a hypermetabolic and catabolic state. Early enteral nutrition maintains the integrity of the gastrointestinal mucosa, has beneficial effects on immunocompetence, and attenuates the metabolic response to stress.[46] A study comparing early (within 36 h) versus delayed enteral nutrition demonstrated a 55% reduction in the risk of infection in human traumatic head injury patients receiving early enteral nutrition.[126] As discussed previously, enteral feeding with concurrent prokinetic therapy is generally well-tolerated in TBI patients and is the preferred method of supplying nutrition. If the patient is unable or unwilling to eat on his/her own, the authors recommend placement of a nasogastric tube. This tube should be passed with as little manipulation and stimulation as possible to avoid coughing and gagging that may increase ICP. Sedation with a benzodiazepine may be used to calm a struggling or resisting patient and assist tube placement. A nasogastric tube is preferred over a nasoesophageal tube so that gastric residual volumes may be measured before each feeding. Thoracic radiography should be performed after tube placement and before feeding to be certain of appropriate tube placement within the stomach. Patients who are unable to protect their airway due to loss of the gag reflex or loss of consciousness are at increased risk for aspiration and may be candidates for parenteral nutrition. IV nutrition may be supplied as total parenteral nutrition or partial parenteral nutrition.

Supportive care

Nursing care is essential for the appropriate management of TBI patients. Frequent turning, provision of clean dry bedding, and physical therapy helps to prevent pressure sores, urine scalding, and limb contraction. Animals may not be able to void voluntarily and so may need their bladder expressed or may need urinary catheterization.[23] Urinary catheterization increases the incidence of urinary tract infections (UTI). The risk of infection increases with preexisting urinary tract disease and is greater in animals with indwelling urinary catheters than in those that are intermittently catheterized. The risk of developing a UTI also increases the longer an indwelling urinary catheter is left in place.[127–130] One prospective study documented bacterial UTIs in >50% of dogs after 4 days with an indwelling catheter.[127] Catheter-induced bacterial UTI may be minimized by using intermittent catheterization when possible, removing the indwelling urinary catheters as soon as possible, using a closed collection system, and using sterile technique when placing and handling the catheter and collection system.[127–130]

Intracranial Pressure Monitoring

Treatment decisions based on ICP measurements rather than on subjective neurologic findings have decreased morbidity and mortality in human TBI patients.[1,2,11,12,34] ICP monitoring is standard procedure for human TBI management. However, the high cost of the fiberoptic monitoring system as well as the technical expertise required for its placement limits its use in veterinary medicine to research and referral practices.[1,11,12,34] An inexpensive and easily implantable epidural ICP monitoring system has previously been evaluated in cats and found to have comparable accuracy to the fiberoptic ICP system.[131] In the future, ICP monitoring may become a more routine and integral part of TBI management in domestic pets.

Diagnostic Imaging

Imaging of a patient's head is indicated when the patient fails to respond to aggressive medical therapy or when the patient deteriorates after initially responding to therapy. Skull radiographs may reveal fractures of the calvaria; however, they do not provide clinically useful information about brain injury.[1] In human head trauma management, imaging with CT is considered standard of care.[9] CT has been the preferred modality due to its availability, rapid scan times, and better visualization of fractures and peracute hemorrhage.[9] Abnormalities noted on CT that are associated with increased ICP include subdural hematomas, subarachnoid hemorrhage, intracerebral hematomas, cerebral infarcts, diffuse brain injury, and generalized cerebral edema often with shift of midline structures and ventricular compression.[46] CT imaging is faster and considerably less expensive than is MRI, and so it has historically also been the preferred imaging modality in

cases of severe head injury in veterinary medicine.[1] In a recent canine study, however, MRI has provided key information relevant to prognosis based upon its ability to detect subtle parenchymal damage that is not evident on CT imaging.[10] The detection of a midline shift and ventricular obliteration indicated a poor prognosis for survival in this study.[10]

Surgical Therapy

In human head trauma patients with elevated ICP refractory to optimal medical therapy more advanced therapeutic options are considered. Options include induction of a barbiturate coma, as discussed previously, or a decompressive surgical procedure such as decompressive craniectomy. However, at this time there is still no consensus as to if and when surgery should be pursued and the effect of surgical intervention on clinical outcome remains unclear. A large randomized multicenter study is currently ongoing to determine whether decompressive craniectomy has a role in the management of human patients with TBI and to evaluate the outcome of those patients undergoing the procedure.[132]

The decision to pursue surgical decompression in veterinary patients should be based on CT or MRI of the brain and consultation with a neurosurgeon.[23] Traditionally, surgical intervention has played a minor role in veterinary head trauma management. However, with the increasing availability of advanced imaging, surgery is beginning to play a relatively larger role. Indications for surgery include open or depressed skull fractures, ongoing hemorrhage, foreign body or hematoma removal, and declining neurologic status despite aggressive medical therapy.[133]

Prognosis

Potential complications associated with TBI include coagulopathies, pneumonia, sepsis, transient or permanent central diabetes insipidus, and seizures.[134] Delayed seizure disorders may develop months to years later as a result of a glial scar seizure focus.[1] While seizures have been reported to complicate between 4% and 42% of cases of severe TBI in human patients,[106] the incidence of seizures in veterinary TBI patients is currently unknown but believed to be low.

Treatment in TBI patients should be immediate and aggressive if the animal is to survive and recover to a level that is functional and acceptable to the owner. The ultimate goal in the management of TBI in veterinary medicine is for the pet to maintain a good quality of life. Many patients can recover if systemic and neurologic abnormalities are identified and treated early. Dogs and cats have a remarkable ability to compensate for the loss of cerebral tissue,[135] making it important to not to make hasty prognostic conclusions based on the initial appearance of a pet suffering from TBI.

Predicting the outcome for an individual patient can be difficult. Multiple prognostic factors have been identified in human medicine. The most important factors identified include age, cause of injury, the Glasgow Coma Scale motor score, pupil response to light, and CT scan characteristics including the presence of subarachnoid hemorrhage. Secondary insults of hypotension and hypoxia have also been found to add important predictive information. Glucose and prothrombin time have been recognized as predictive laboratory parameters.[136] Information on prognostic indicators in veterinary medicine is scarce. The MGCS has recently been correlated with probability of survival in the first 48 hours after TBI in dogs. MGCS predicted a 50% probability of survival in a patient with a score of 8 out of a total of 18. This same study found that gender, weight, age, and presence of skull fractures did not predict survival. This study, however, excluded patients with systemic abnormalities.[5] Concurrent injuries are commonly seen in dogs suffering TBI. As such, the MGCS must be utilized with discretion when estimating prognosis in those patients enduring multiple injuries. The effectiveness of specific treatments and prognosis will likely always be difficult to assess due to the multifactorial nature of traumatic injuries.

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