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Neurological Emergencies

Mini Series

Session One - Acute Brain Disease –

Head trauma and Status Epilepticus

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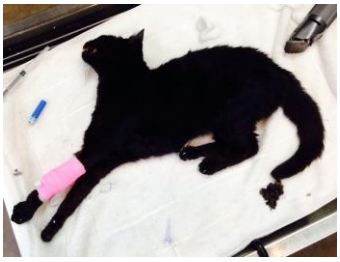

INTRODUCTION

Severe head trauma is associated with high mortality in human beings and animals. Although there is no standard of care for head trauma in human medicine, a series of guidelines have been developed centered around maintaining adequate cerebral perfusion. The appropriate therapy for head trauma patients remains controversial in veterinary medicine due to a lack of objective information on the treatment of dogs and cats with head injuries. Treatment of affected animals must be immediate if the animal is to recover to a level that is both functional and acceptable to the owner. Many dogs and cats can recover from severe brain injuries if systemic and neurological abnormalities that can be treated are identified early enough.

PATIENT ASSESSMENT

As with all types of acute injury, the "ABCs" (airway, breathing, cardiovascular status) of emergency care are extremely important. Initial physical assessment of the severely brain-injured patient focuses on imminently life threatening abnormalities. It is important not to focus initially on the patient's neurological status as many patients will be in a state of hypovoLemic shock following a head injury, which can exacerbate a depressed mentation. Hypovolemia and hypoxemia need to be recognized and addressed immediately. In addition, a minimum essential data-base includes a PCV, total protein level, a blood urea level, and electrolyte levels as well as a urine specific gravity. Specific attention should also be paid to the serum glucose levels as hyperglycemia has been demonstrated to be related to head trauma severity, although unlike in humans, a specific association with outcome has not yet been demonstrated. Respiratory system dysfunction can be common after head injury. The most dramatic respiratory abnormality seen following head injury can be neurogenic pulmonary edema. Neurogenic pulmonary edema is usually self-limiting if the patient survives, and will resolve in a matter of hours to days, but can cause severe dyspnea, tachypnea and hypoxemia. Hypoxemia exacerbates the development of secondary tissue damage.

Neurological Assessment

Neurological assessment should be repeated every 30 to 60 minutes in severely head injured patients to assess the patient for deterioration or to monitor the efficacy of any therapies administered. This requires an objective mechanism to 'score' the patient so that treatment decisions could be made logically.

MEDICAL THERAPY

1. Minimizing increases in ICP

Simple precautions can be taken in positioning the animal with its head elevated at a 30° angle from the horizontal to maximize arterial supply to and venous drainage from the brain. It is also important to ensure that there is no constrictive collar obstructing the jugular veins as this immediately elevates ICP.

2. Fluid therapy

The basic goal of fluid management of head trauma cases is to maintain a normovolemic to slightly hypervolemic state. There is no support for attempting to dehydrate the patient in an attempt to reduce cerebral edema and this is now recognized to be deleterious to cerebral metabolism. In contrast immediate restoration of blood volume is imperative to ensure normotension and adequate CPP. Initial resuscitation usually involves intravenous administration of hypertonic saline and or synthetic colloids. Use of these solutions allows rapid restoration of blood volume and pressure while limiting volume of fluid administered. In contrast, crystalloids will extravasate into the interstitium within an hour of administration and thus larger volumes are required for restoration of blood volume. As a result this could lead to exacerbation of edema in head trauma patient. Hypertonic saline administration (4-5 ml/kg over 3-5 minutes) draws fluid from the interstitial and intracellular spaces into the intravascular space which improves blood pressure and cerebral blood pressure and flow, with a subsequent decrease in intracranial pressure. However, this should be avoided in presence of systemic dehydration or hypernatremia and it should be noted that the effects of this fluid only last up to an hour. Colloid solutions, such as Dextran-70 or Hetastarch should be administered after hypertonic saline is used, to maintain the intravascular volume. Hypertonic solutions act to dehydrate the tissues, thus it is essential that crystalloid

solutions are also administered after administration of HSS to ensure dehydration does not occur. The sole use of colloids will not prevent dehydration; in addition, the co-administration of hypertonic solutions and colloids are more effective at restoring blood volume than either alone.

3. Osmotic diuretics

Osmotic diuretics such as mannitol are very useful in the treatment of intracranial hypertension. Mannitol has an immediate plasma expanding effect that reduces blood viscosity, and increases cerebral blood flow and oxygen delivery. This results in vasoconstriction within a few minutes causing an almost immediate decrease in ICP. The better known osmotic effect of mannitol reverses the blood-brain osmotic gradient, thereby reducing extracellular fluid volume in both normal and damaged brain. Mannitol should be administered as a bolus over a 15 -minute period, rather than as an infusion in order to obtain the plasma expanding effect; its effect on decreasing brain edema takes approximately 15-30 minutes to establish and lasts between 2 and 5 hours. Administering doses of 0.25 g/kg appear equally effective in lowering ICP as doses as large as 1.0 g/kg, but may last a shorter time. Repeated administration of mannitol can cause an accompanying diuresis, which may result in volume contraction, intracellular dehydration and the concomitant risk of hypotension and ischemia. It is therefore recommended that mannitol use is reserved for the critical patient (Glasgow coma score of < 8) or the deteriorating patient. There has been no clinical evidence to prove the theory that mannitol is contraindicated in the presence of intracranial hemorrhage. There is contradictory evidence that the combination of mannitol with furosemide (0.7 mg/kg) may lower ICP in a synergistic fashion, especially if furosemide is given first.

4. Oxygenation and ventilation

Hyperoxygenation is recommended for most acutely brain-injured animals. Partial pressure of oxygen in the arterial blood (PaO_2) should be maintained as close to normal as possible (at or above 80 mm Hg). Supplemental oxygen should be administered initially via face-mask as oxygen cages are usually ineffective as constant monitoring of the patient does not allow for a closed system. As soon as possible, nasal oxygen catheters or transtracheal oxygen catheters should be used to supply a 40% inspired oxygen concentration with flow rates of 100 ml / kg / min and 50 ml / kg / min respectively. If the patient is in a coma, immediate intubation and ventilation may be needed if blood gas evaluations indicate. A tracheostomy tube may be warranted in some patients for assisted ventilation. Hyperventilation has traditionally been known as a means of lowering abnormally high ICP through a hypocapnic cerebral vasoconstrictive effect. However, hyperventilation is a double-edged sword. Besides reducing the ICP, it induces potentially detrimental reductions in the cerebral circulations if the pCO_2 level is less than 30-35 mmHG. The major difficulty with hyperventilation is our present inability to monitor the presence and effects of ischaemia on the brain. It is important that animals do not hypoventilate, and such animals should be ventilated to maintain a $PaCO_2$ of 30-40mmHg. Aggressive hyperventilation can be used for short periods in deteriorating or critical animals.

5. Seizure prophylaxis

Although the role of prophylactic anticonvulsants in preventing post-traumatic epileptic disorders remains unclear, seizure activity greatly exacerbates intracranial hypertension in the head injury patient. For this reason, it is recommended to treat all seizure activity in these patients aggressively but not prophylactially. As most cases need to be treated parenterally, phenobarbital (2 mg/kg IM q 6-8hrs) is recommended. This can be continued for 3-6 months after the trauma and can then be slowly tapered off if there have been no further seizures. Phenobarbital will have the additional benefit of reducing cerebral metabolic demands and therefore acts as a cerebral protectant.

6. Corticosteroids

Corticosteroids, known to be beneficial in brain edema attributed to a tumor, have been studied extensively in head injury. Clinical trials in people have not shown a beneficial effect of corticosteroids, including methylprednisolone sodium succinate, in the treatment of head injury. In fact, they are now contraindicated based on an increased incidence of mortality following their use. In addition, they have

been associated with increased risks of infection, are immunosuppressive, cause hyperglycemia and other significant effects on metabolism.

SURGICAL THERAPY

A description of the surgical techniques for intracranial surgery can be found elsewhere. Although it is rare that surgery is indicated in head injury cases, there are several specific abnormalities that can be associated with an episode of head trauma that may warrant the consideration of surgical treatment:

Acute extra-axial Hematomas

Generous craniotomies are generally indicated once these abnormalities have been diagnosed with imaging. If the hematoma is due to a fracture across a venous sinus, there may be profuse bleeding associated with surgical intervention. The need for blood transfusions should be expected. Hematoma removal also risks the chance of bleeding from previously compressed vessels.

Calvarial Fractures

A skull fracture *per se* may or may not have significant implications for patient management. Skull fractures are typically differentiated based upon pattern (depressed, comminuted, linear); location; and, type (open, closed). A fracture is generally classed as depressed if the inner table of the bone is driven in, to a depth equivalent to the width of the skull. All but the most contaminated, comminuted and cosmetically deforming depressed fractures can be managed without operative intervention.

Acute Intraparenchymal Hematoma

In contrast to acute extra-axial hematomas, acute intraparenchymal clots may be conservatively managed, unless subacute enlargement of initially small intraparenchymal clots is identified with repeat MR scanning.

Hemorrhagic Parenchymal Contusions

Most hemorrhagic contusions do not require surgical management. The main indication for surgery with these types of lesions is limited to cerebellar contusions with compression of the 4th ventricle and brain stem; surgery aims to reduce the potential for further compression and herniation, which can develop over the initial 24-48 hours.

Intracranial Hypertension (ICH)

Benefit can be found when decompressive procedures are carried out before irreversible bilateral papillary dilation has developed. Conversely, “prophylactic” decompressive surgery seems inappropriate before non-surgical management of elevated ICH has been carefully maximized.

Status Epilepticus - a practical guide to managing emergency seizures

The goals of anticonvulsant therapy in SE are to achieve cessation of clinical and electrical seizure activity and prevent its recurrence. Intravenous drug treatment for SE should be started without delay. This is necessary based upon the relationship between duration of SE and the extent of neurologic morbidity. This approach is also based upon experimental animal models that suggest that SE becomes progressively less responsive to treatment with diazepam.

Diazepam

Diazepam remains the first drug of choice for the treatment of SE in dogs and cats. With its relatively brief duration of action, diazepam is not a definitive therapy for SE. It has been recommended to use 0.5 to 1.0 mg/kg intravenously, up to a maximum dose of 20 mg, in dogs and cats. This dose can be repeated to effect or twice within two hours. If the diazepam does not control the seizures, the use of phenobarbital should be considered. Probably the most common and most dangerous error made in the management of SE is to treat repeated seizures with repeated doses of IV diazepam without administering an adequate loading dose of a longer-acting anti-epileptic drug. In this situation, the patient will continue to have seizures, toxic concentrations of diazepam or diazepam metabolites will accumulate, and serious morbidity may result from diazepam over-dosage. Intravenous administration of diazepam may not be possible in some patients. It can be administered intramuscularly (IM), although absorption is not predictable. Rectal administration of diazepam may be considered initially at a dose of 0.5 to 2.0 mg/kg body weight depending upon whether the animal was being treated with phenobarbitone before the onset of SE. It may be necessary to use the higher dose in dogs receiving long-term phenobarbitone therapy. In previously untreated dogs, a per rectum diazepam dose of 1 mg/kg results in a mean time to peak plasma concentration of approximately 14 minutes.

Midazolam

Midazolam is a recently developed water-soluble benzodiazepine which is biotransformed by hepatic microsomal oxidation followed by glucuronide conjugation. Midazolam has been shown to have a wide margin of safety and a broad therapeutic index. Unlike diazepam, with erratic and incomplete intramuscular absorption, midazolam is rapidly absorbed following IM injection, with a high bioavailability, an early onset of sedation, and early clinical effects. The peak plasma concentration in dogs after IM administration was seen within 15 minutes. The dose for cats and dogs is 0.066 - 0.3 mg/kg IM or IV.

PHENOBARBITAL

Phenobarbital (PB) is a safe, inexpensive drug that may be administered orally, intravenously or intramuscularly. Phenobarbital increases the seizure threshold required for seizure discharge and acts to decrease the spread of the discharge to neighboring neurons The recommended loading dose is 12 to 24 mg/kg IV, if immediate therapeutic concentrations are desired but this can induce a profound stupor with concurrent suppression of the cardiovascular and respiratory. Alternatively, the dose can initially be 2 mg/kg IV, repeating the dose every 20 - 30 minutes to effect and to a maximum total 24-hour dose of 24 mg/kg. The parenteral form can also be given IM, which is recommended if diazepam has already been administered. This will avoid the potentiation of profound respiratory and cardiovascular depression. The depressant effects of PB on respiratory drive, level of consciousness, and blood pressure may complicate management of the SE patient, especially when administered after benzodiazepine.

Propofol

In human cases of refractory SE, the use of IV infusions of anesthetic doses of propofol, 2,6-diisopropylphenol, has become standard. This approach has recently been evaluated in veterinary patients. Propofol has barbiturate- and benzodiazepine-like effects on the (GABA)A receptor and can suppress CNS metabolic activity. Propofol can be administered by IV bolus (1-4 mg/kg) or by constant rate infusion (0.1-0.6 mg/kg/min titrated to effect or up to 6 mg/kg/hr). The advantages of this drug over the barbiturates are its rapid clearance, chiefly eliminated by hepatic conjugation to inactive metabolites, and less profound hypotensive effects. However, this drug should be used with caution, preferably in settings where definitive airway control and hemodynamic support is possible, as hypoxemia secondary to apnoea is a primary side-effect as is myocardial depression.

Levetiracetam

Levetiracetam is the *S*-enantiomer of the ethyl analogue of piracetam that has broad-ranging, unique but incompletely understood mechanisms of action against seizures. Its main mechanism may be in decreasing the onset of a seizure through enhanced GABA activated Cl^- conductance. The pharmacodynamic effect is believed to outlive the known half-life of the drug. In dogs, this drug has a half-life is approximately 4-6 hours, is liver cytochrome P450 independent and is excreted unchanged by the kidneys. The dose range documented for dogs is estimated to be 5-25 mg/kg q 8-12hrs PO. Levetiracetam has been documented as the most well tolerated anti-epileptic drug in humans, with adverse reactions equal to that of placebo. Overall, this drug is proven to be a highly effective adjunctive therapy in humans to control seizures. In 2006, levetiracetam was approved in humans as the first of the newer anticonvulsive drugs for intravenous administration and has been trialed for its use with status epilepticus. It has been shown that it is an effective drug in people with this condition and is well tolerated at high doses. Recent pharmacokinetic studies in dogs have demonstrated that IV administration of this drug is well tolerated when administered as a bolus at 60 mg/kg and rapidly achieved suggested therapeutic levels. Clinical veterinary trials are underway for this drug.

Ketamine

Experimental animal work has indicated that NMDA glutamate receptor antagonists may be used to treat the so called self-sustaining status epilepticus (SSSE). This type of status exists after approximately 10 minutes to 1 hour and may have a different underlying pathophysiology to that of the initial SE in that NMDA receptors may be over stimulated by excessive glutamate concentrations. Ketamine is a NMDA receptor antagonist which has been used in humans with refractory or SSSE and has been shown to be effective in a dog with SSSE.

Inhalational Anesthesia

Inhalational anesthetics have been recommended as a last resort in cases of resistant SE. The equipment and personnel necessary to administer inhalational anesthesia may not be readily available and can be cumbersome. Isoflurane, an inhalational general anesthetic agent, may be efficacious in the treatment of resistant SE. Not all of the volatile anesthetic agents have anti-epileptic potential, however; enflurane may actually increase seizure activity. Isoflurane does not undergo hepatic metabolism, has a rapid onset of action and has been extensively studied. Obviously, isoflurane therapy necessitates ventilation and intensive-care monitoring, and hypotension may occur during therapy.