https://doi.org/10.17221/20/2017-VETMED

Traumatic brain injury in dogs and cats: a systematic review

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ABSTRACT: Traumatic brain injury occurs frequently in dogs and cats due to motor vehicle accidents, falls and crush injuries. The primary lesion occurs at the time of injury and causes direct, irreversible damage to the brain parenchyma and vasculature. Secondary lesions occur in the minutes following the trauma due to a combination of physical and biochemical changes that lead to intracranial hypertension. Therefore, knowing the pathophysiology of the cranioencephalic trauma is essential for treatment directed at minimising secondary damage. The approach to the patient affected by traumatic brain injury is based on the ABCD of trauma, guided by the neurological examination with the aid of imaging exams and adequate therapeutic measures. The treatment of patients with cranioencephalic trauma is still in many ways controversial. For that reason, this literature review aims to address the main points regarding the pathophysiology of this disease and to describe the clinical and surgical therapeutic options currently available.

Keywords: head injury; small animals; pathophysiology; treatment

Contents

1. Pathophysiology

An understanding of the pathophysiology is essential in guiding and evaluating treatment success in traumatic brain injury (TBI). High-speed injuries involving rapid acceleration and deceleration, especially when there is no rotating element, result in shear forces at the border between the white matter and the grey neocortical matter. This shear force can cause generalised lesions in the axonal structure, known as diffuse axonal lesions (DAL), which are a determinant for cerebral oedema (Helmy et al. 2007). The damage resulting from this injury can be separated into two categories, chronologically divided into primary and secondary injury.

1.1 Primary injury

The primary injury occurs immediately after trauma as a direct consequence of the physical insult. Its extent depends on the type and intensity of

https://doi.org/10.17221/20/2017-VETMED

the impact force and can involve inevitable and intractable damage to the cerebral parenchyma, such as surface contusions (i.e. bruising where the pia is intact; O'Connor et al. 2011), bruises, haemorrhage, lacerations (i.e. where the pia is torn; O'Connor et al. 2011) and DAL, (Czosnyka and Pickard 2004; Portella et al. 2005; Helmy et al. 2007). The most severe forms of primary brain injury are lacerations, and vasogenic oedema may also occur if there is a direct vascular injury followed by intracranial haemorrhage. The occurrence of cranial fractures can generate cerebral trauma that damages the parenchyma and blood vessels, making clinical management impossible and increasing the odds that the patient will die (Sande and West 2010; Dewey and Fletcher 2015). Hence, the professional must be able to adequately prevent, recognise and treat secondary injuries (Sande and West 2010) since primary injury is essentially an irreversible event (O'Connor et al. 2011).

1.2 Secondary injury

Secondary lesions occur in the minutes or even days following trauma and involve the activation of several biomechanical mechanisms that together act to perpetuate brain lesions and whose course is a determining factor for the patient's prognosis (Sande and West 2010). The main determinants of high mortality in TBI are the severity of the primary lesions and complications from the secondary lesions that cause cerebral ischaemia triggering intracranial hypertension, systemic hypotension, hypoxia, hyperpyrexia, hypercapnia, hypoglycaemia and a focal lesion, such as subdural haematoma, that is an indicative of a lesion in the brain parenchyma (Helmy et al. 2007). Another aggravating factor is multiple trauma with haemorrhage and brain oedema that are responsible for the appearance of secondary autolytic processes that eventually lead to death (Rabelo et al. 2010).

Cerebral oedema may be due to a non-specific response to brain insults such as trauma, cell damage and ischaemia that can disturb Starling's law. Starling's law states that the greater the volume of blood received by the ventricle during diastole, the greater the blood volume ejected into the arteries during systole. Thus, imbalances in Starling's law can lead to accumulation of fluid in the brain parenchyma, worsening the oedema (Varella-Hernandez et al. 2002). From a physiological and morphological point of view, this accumulation of fluid in the encephalon can generate a vasogenic oedema (Klatzo 1994). Vasogenic oedema occurs due to direct vascular damage, causing an increase in vascular permeability and consequent extravasation of plasma fluids and proteins out into the intravascular space, which then accumulate in the cerebral parenchyma, causing an increase in volume (Varella-Hernandez et al. 2002).

Physical insults can trigger an inflammatory process in the central nervous system due to the loss of stability of the blood-brain barrier, which is essential in regulating the access of cells and macromolecules from the periphery to the central nervous system. Lymphocytes, macrophages and microglia cells are potent generators of reactive molecules and mediators of inflammation such as adhesion molecules, metalloproteinases, chemokines and cytokines. The combination of systemic insults, such as pneumothorax, haemothorax, rib fractures, pulmonary contusions and intracranial physical and biochemical changes are responsible for the genesis of secondary lesions such as haematomas, intracranial hypertension, infection, hypoxia, oedema and cerebral ischaemia. Axial haematomas within the cerebral parenchyma and extra-axial subarachnoid, subdural and epidural haematomas lead to compression of the brain with subsequent neurological dysfunction (Vandevelde 2004).

Physical trauma triggers biochemical pathways that work together to perpetuate damage to brain tissue. Secondary intracranial injury is mediated by increased activity of excitatory neurotransmitters such as glutamate and aspartate, which are released in large quantities immediately after trauma, accelerating metabolic activity and subsequently leading to depletion of ATP (adenosine triphosphate), with consequent failure of the sodium and potassium (Na/K) pump and intracellular calcium and sodium accumulation in the neurons. Depolarisation leads to a greater release of the aforementioned neurotransmitters which mediate further increases in intracellular calcium through secondary messengers and proteolytic enzymes, creating an osmotic gradient and promoting water diffusion. This event is called cytotoxic oedema. Other factors responsible for the genesis of secondary lesions are the generation of reactive oxygen species and the release of inflammatory cytokines. Reactive oxygen species arise due to local tissue

https://doi.org/10.17221/20/2017-VETMED

acidosis and hypoperfusion and are detrimental to cell membranes; particularly destructive are hydroxyl radicals, which have a great capacity to remove hydrogen atoms from the methylene group of polyunsaturated fatty acids, thereby initiating lipid peroxidation. The resulting oxidation of lipids in the cell membrane alters permeability and leads to dysfunction. As brain tissue is rich in lipids, it is particularly susceptible and sensitive to oxidative injury. The release of cytokines activates the arachidonic acid cascade and the coagulation cascade, destabilising the blood-brain barrier and inducing nitric oxide production. This is responsible for excessive vasodilatation, leading to loss of pressure autoregulation (Varella-Hernandez et al. 2002; Sande and West 2010).

The relationship between volume and intracranial pressure is non-linear. The Monro-Kellie doctrine states that the skull is a closed, inelastic compartment containing three components, cerebral parenchyma (80%), arterial and venous blood (10%) and cerebrospinal fluid (10%), that under normal circumstances exist in a state of dynamic equilibrium. An increase in the volume of any of these components should be compensated for by a decrease in one or more of the others; otherwise, an increase in intracranial pressure is unavoidable (Sande and West 2010). When compensatory mechanisms fail to maintain the equilibrium between these components, there is an increase in intracranial volume, which causes compression of the cerebral vasculature with consequent intracranial hypertension and reduced cerebral blood flow (CBF). There is then an increase in carbon dioxide, which is locally detected at the vasomotor centre, and which then initiates a sympathetic nervous system response that results in increased ejection volume and heart rate. This results in increased mean arterial pressure (MAP) in an attempt to increase cerebral perfusion pressure (CPP). Systemic hypertension is detected by baroreceptors, located in the walls of the carotid arteries and aortic arch, resulting in a reflex bradycardia. This mechanism is known as the cerebral ischaemic response or the Cushing reflex (Dunn 2002; Laffey and Kavanagh 2002; Portella et al. 2005; Stocchetti et al. 2005; Sande and West 2010).

The mechanism behind cerebral compliance is essential to avoid an increase in intracranial pressure. Cerebral perfusion pressure should be kept close to normal since low levels are detrimental to intracranial volume balance. CPP can be defined in the following formula:

$$CPP = MAP - ICP$$

where: CPP = cerebral perfusion pressure; MAP = mean arterial pressure; ICP = intracranial pressure

Thus, blood pressure is important to maintain CBF, especially in circumstances where cerebrovascular autoregulation has been impaired, such as after TBI. However, even if autoregulation is intact, changes in blood pressure and intracranial pressure may alter blood volume as a result of dilation or constriction of cerebral blood vessels (Dunn 2002; Rabelo et al. 2010; Cooper et al. 2011). CPP is the main determinant of cerebral blood flow and thus, brain oxygenation and nutritional support depend on it (Vandevelde 2004).

Although the brain constitutes only 2% of the body weight, it consumes 15% of cardiac output, 20% of inhaled oxygen and more than 25% of glucose. There are two phases in CBF autoregulation which together ensure the constancy required for the fulfilment of the oxygen and glucose requirements of brain tissue. The first one, related to autoregulation of blood pressure, allows maintenance of CBF during constant variations of MAP between 50 and 120 mm Hg. Thus, increases in MAP leads to vasoconstriction and decreased vasodilation in the brain. These changes occur due to logarithmic vasoreactivity to changes in CPP. The second phase is metabolic autoregulation in response to hypercapnia, which causes vasodilation, decreased cerebral vascular resistance and hypoxia. Levels of O_2 lower than 60 mm Hg induce vasodilation, thus increasing CBF (Yates and Roberts 2000). CBF increases with vasodilation and decreases with constriction of cerebral arterioles, termed cerebral resistance vessels. These vessels respond to changes in systemic blood pressure (autoregulation of pressure), blood viscosity (autoregulation of viscosity) and metabolic demand, keeping CBF levels within the limits that are appropriate to meet the metabolic demands of brain tissue (Varella-Hernandez et al. 2002).

The intravascular pressure and its effect on cerebral blood volume not only affects intracranial pressure, but also the mechanical properties of the brain and the capacity of the intracranial space to "fit" in its place, and low levels of blood can be detrimental to the intracranial volume balance (Rabelo

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et al. 2010). The CPP acts as the pressure gradient that acts on the cerebrovascular circulation, and so it is important in the regulation of the CBF and required to keep it at constant levels (Dunn 2002).

2. Patient assessment

Due to the scarcity of prospective or retrospective clinical data in the veterinary literature, treatment recommendations for dogs and cats with TBI are mainly based on human and experimental studies. Also, trauma patients are usually polytraumatised and the initial approach to trauma should be based on ABCD (airway, breathing, cardiovascular condition and neurological dysfunctions) and clinical approach (anamnesis, physical examination, neurological examination, stabilising the patient and complementary exams). For this reason, emergency management is critical to stabilise the patient and should be directed towards optimising cerebral perfusion and oxygenation and avoiding secondary injury (Menon 1999; Platt and Olby 2004; Assis 2005; Dewey and Fletcher 2008; Gomes and Neutel 2008). The modified Glasgow coma scale (da Costa and Dewey 2015) was adapted to veterinary medicine in order to classify the neurological status of a patient with TBI and perform serial monitoring over a 72-hour period (Platt 2008). This scale is divided into three categories of neurological examination consisting of level of consciousness, motor activity and brainstem reflexes, and each category can receive a score of one to six points, giving a total of three to 18 points. The best prognosis is associated with the highest score, and low scores are associated with a high mortality rate, with less than 50% chance of survival in a 72-hour period (Platt and Olby 2004). This scoring system provides an estimate of the initial assessment, response to treatment, evaluates therapeutic choices and provides a prognosis.

After the initial approach focusing on the trauma, patient stabilisation and initial evaluation using the modified Glasgow coma scale, anamnesis should be performed, consisting of logical and direct questions aiming at finding the cause of the trauma, the mental state soon after injury, whether seizures are present, whether there was emesis and whether the patient was able to walk immediately after trauma. Once these questions have been answered, the clinician must start the physical examination. This should be done methodically and meticulously, avoiding excessive manipulation of the head, neck and vertebral column because the patient may have lesions and/or fractures that have not been detected. The examination should be initially carried out using an otoscope, in order to verify the integrity of the tympanic membrane. The presence of a clear fluid, hyaline, often mixed with blood, can be determined by investigating flow in the external acoustic meatus or through the nostrils, which characterise otoliquorrhea and rhinoliquorrhea, respectively. These are associated with violent trauma that affect the bone at the base of the skull and are suggestive of fracture with formation of cerebrospinal fluid fistula due to simultaneous rupture of the meninges. Also, hemotympanum may be found associated with fracture of the temporal bone. Ophthalmoscopy should also be performed to diagnose scleral bleeding, an important finding in patients with TBI, since it may reflect cerebral and/or meningeal haemorrhage (Laffey and Kavanagh 2002; Stocchetti et al. 2005).

Animals with TBI may exhibit clinical signs similar to those with a multifocal neurological syndrome, as there may be lesions in various compartments of the brain. These types of lesions can generate different behavioural states, ranging from completely normal appearance after a short period of unconsciousness to coma, stupor, delirium or depression (Syring et al. 2001; Braund 2003). The neurological evaluation of the patient should consist of a cautious evaluation of the patient's state of consciousness (AVPU Scale), respiratory pattern, pupil size and responsiveness, ocular position and movement, muscle tone, proprioceptive tests when possible, evaluation of cranial nerves and the search for a possible pain focus (Bagley 2005; Sande and West 2010). The AVPU scale (Table 1) has fewer variables than the Glasgow coma scale and consists of assessing the patient's state of consciousness by classifying their clinical status using scores from 1 to 4: the patient is alert, the patient responds to verbal stimulation, the patient responds to painful stimuli, the patient does not respond (Rabelo

Table 1. AVPU Scale (Adapted from Rabelo 2008)

Score	State of consciousness
A-1	the patient is alert
V-2	the patient responds to verbal stimulation
P-3	the patient responds to painful stimuli
U-4	the patient does not respond

https://doi.org/10.17221/20/2017-VETMED

2008). The modified Glasgow coma scale, however, not only evaluates the patient's state of consciousness, but also takes into account motor activity and brainstem reflexes. A neurological evaluation should be performed, preferably before administration of any drugs with a sedative effect, to determine the location of the lesion as well as its severity and evolution. Imaging may also help in this stage, especially in animals that are not responsive to drug treatment (Siqueira et al. 2013; Dewey and Fletcher 2015).

Computed tomography (CT) is the diagnostic method of choice for patients with TBI, since images are obtained faster compared to magnetic resonance imaging (MRI) and there is better visualization of acute haemorrhages and bone structures, providing fundamental information to determine the prognosis (da Costa and Dewey 2015). On CT, haemorrhage appears as hyperattenuating (hyperdense) in the acute stages, and over time, its density decreases with clot resorption, creating a hypoattenuating lesion which could be confused with brain oedema (Platt et al. 2016). Conversely, CT might present some disadvantages, such as exposure to ionising radiation, poor soft tissue detail and poor visualisation of brain and subtle parenchymal lesions that are better observed on MRI (da Costa and Dewey 2015). The identification of haematomas or haemorrhage, parenchymal contusions and oedema are easily identified on MRI. This diagnostic method provides better visualisation of subtle parenchymal changes and provides valuable information to facilitate the prognosis (Platt et al. 2016).

Radiographic examination is also important in the diagnosis of TBI, since pulmonary haemorrhage, pulmonary contusion and pneumothorax may be present in the thorax, but it is not useful in the identification of brain lesions and may only reveal the presence of fractures with depression of the calvaria (Branco 2011; Siqueira et al. 2013). Spinal radiographs may also be essential in patients with TBI, as it aids in the detection of spinal injuries (Silva 2013).

Laboratory analyses include haematological and biochemical analyses that vary with clinical presentation of the patient, blood gas analysis, serum electrolytes and serum osmolarity (Silva 2013). Collection of cerebrospinal fluid is contraindicated because if the patient has an elevated intracranial pressure, puncture favours encephalic herniation (Branco 2011).

3. Treatment

Treatment for traumatic brain injury is still controversial and also still based on human and experimental studies as well as on the personal experiences of professionals. The Brain Trauma Foundation (BTF), in collaboration with the American Association of Neurological Surgeons, has established that insufficient data does not permit standardisation of treatment for TBI or a single treatment guideline in terms of initial patient assessment. It is based, however, on resuscitation and quick stabilisation of the patient, which should follow five principles: normocapnia, normoxia, normotension, normothermia and normoglycaemia (Braund 2003; Girling 2004; Platt and Olby 2004; Dewey and Fletcher 2008; Sande and West 2010; Dewey and Fletcher 2015).

3.1 Intracranial pressure control

The most frequent cause of death and disability in animals with traumatic brain injury is elevated intracranial pressure, as this leads to dysfunction of blood flow in the brain, causing hypoxia and ischaemia (Lubillo et al. 2009; Cecil et al. 2011).

A simple but effective procedure to aid the control of intracranial pressure is to position the patient's head at a 30-degree angle to the body, which provides a greater arterial supply to the brain, as well as greater venous drainage (Figure 1). Care must be taken to not compress the jugular vein since this leads to an immediate increase in intracranial pressure (Platt 2008). Care should also be taken to position the head properly by placing a support just below the head in order to decrease the chances of aspiration into the lower airways leading to complications, since these patients are predisposed to regurgitation. Therefore, it is preferable to elevate the head of the animal by placing a support under its shoulders, so in case of reflux, the contents may be expelled out of the mouth (Opperman 2014).

3.2 Fluid therapy

Fluid therapy has the objective of creating a state of normovolemia or a mild state of hypervolemia since the restoration of the blood volume is essential in the control of the tension and pressure of

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Figure 1. Stray cat with traumatic brain injury caused by car accident
Reproduced with permission from the University Veterinary Hospital of the Federal University of San Francisco Valley. The patient was in an incubator to maintain body temperature and oxygen therapy. The head was elevated to a 30-degree angle, providing greater arterial supply to the brain as well as greater venous drainage

cerebral perfusion. There is usually concern about the aggressive use of fluid therapy in hypotensive patients on the basis that this could worsen the cerebral oedema; however, studies refute this theory and state that the use of fluid therapy in the patient with brain injury is beneficial for the oedematous brain, even if high volumes of crystalloids are used (Dewey and Fletcher 2015).

Initial resuscitation is performed with the use of hypertonic saline solutions or synthetic colloids, as they allow a rapid return to normal blood volume and blood pressure while limiting the volume of fluid administered. Hypertonic saline solution has shown excellent results in the initial resuscitation of patients with TBI, and its recommended dose is 4 to 6 ml/kg of 7.5% NaCl for 10 to 15 minutes. If an artificial colloid is added, the effect of the hypertonic saline solution is prolonged for hours. In cases of shock, synthetic colloids should be given at a dose of 10–20 ml/kg, to effect (Dewey and Fletcher 2008; Sande and West 2010; Rainey and Odunayo 2015). If the patient presents severe anaemia, it is recommended to transfuse with whole blood or packed red blood cells, so that blood volume is maintained and tissue hypoxia is prevented. The haematocrit should be increased from 25 to 30% in order to achieve the purpose of this therapy (Dewey and Fletcher 2008; Sande and West 2010; Lorenz et al. 2011).

The use of isotonic crystalloids is less efficient when compared to the hypertonic ones, since they rapidly suffer extravasation to the interstitium, requiring a greater volume to restore blood volume, which may exacerbate the patient's cerebral oedema (Platt 2008). However, isotonic crystalloids can be used to replace diuresis caused by some drugs, such as mannitol, and to tackle the dehydration caused by the use of hypertonic solutions, with doses of at most 90 ml/kg/h for dogs and 40 to 60 ml/kg/h for cats (Verneau 2005). The use of solutions containing glucose is contraindicated since the patient with cranioencephalic trauma presents deficient tissue oxygenation and this could lead to the formation of lactic acid by anaerobic glycolysis in turn causing metabolic acidosis (Fernandez and Bernardino 2010).

3.3 Oxygenation

Oxygenation is a highly recommended therapeutic method in patients with TBI to maintain the partial pressure of oxygen (PO_2) in arterial blood as close as possible to normal (80 mm Hg). Oxygen can initially be offered to the patient via a mask, but this may subject the animal to stress and is inefficient for patient monitoring. It should be replaced by a nasal catheter that may only be placed close to the nostrils and not introduced, or a transtracheal tube, through which oxygen at 40% concentration is provided at flow rates of 100 ml/kg/min and 50 ml/kg/min, respectively. If in a comatose state, the patient should be immediately intubated and ventilated according to the needs

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indicated by blood gas analysis (Platt 2008; Dewey and Fletcher 2015).

Although hyperoxygenation is recommended for patients with TBI, caution should be taken, as studies have reported adverse effects that include changes in non-damaged tissues, cerebral hyperoxic vasoconstriction, inhibition of metabolic enzymes and formation of free oxygen radicals (Floyd et al. 2003; Magnoni et al. 2003; McLeod et al. 2003). Recent studies have demonstrated that extreme hyperoxaemia in a patient with head injury is inefficient in accelerating the recovery process and may, through several mechanisms, increase brain injury (Davis et al. 2009).

Hyperbaric oxygen therapy is a therapy that is currently gaining in popularity for the treatment of neurologic diseases; it consists of inhaling 100% oxygen under pressures greater than 1 absolute atmosphere (ATM). Studies in experimental models have shown that this procedure is capable of inhibiting apoptosis and suppressing inflammation, thus protecting the integrity of the blood-brain barrier and promoting angiogenesis and neurogenesis with pressures below 3 ATM, but its clinical efficacy is still controversial in humans because of the heterogeneity of TBI (Braswell and Crowe 2012; Sanchez 2013; Hu et al. 2016).

3.4 Osmotic diuretics

Hyperosmotic therapy consists of the administration of a substance that can create an osmotic gradient that makes the water from the extracellular and intracellular compartments move into the vessels. This osmotic gradient will therefore promote a reduction in intracranial pressure by reducing intracranial volume and improving complacency (Raslan and Bhardwaj 2007).

Mannitol is classified as an osmotic diuretic. Its main and most efficient mechanism of action is the promotion of the vasoconstriction reflex through a reduction in blood viscosity, which reduces intracranial pressure. Another mechanism of action of mannitol is a decrease in the production of cerebrospinal fluid, and the difference in osmolarity leads to drainage of extravascular fluid into the intravascular space, reducing oedema (Dewey and Fletcher 2015). The vasoconstriction reflex occurs in a few minutes and is faster than the osmotic effect caused by mannitol. This drug is administered exclusively intravenously, and it is excreted by the kidneys without being metabolised or resorbed in the tubules. Its administration dose is 0.5 to 2 g/kg in bolus, but slowly, in a range of 15 to 20 minutes, every 3 to 6 hours, with a maximum of three boluses in 24 hours, at room temperature, preferably using a filter to prevent the formation of crystals (Gomes 2011; Dewey and Fletcher 2015; Rainey 2015).

Complications associated with the use of mannitol in the treatment of TBI involve renal and neurological impairment. When it is used repeatedly at osmolarity values that exceed 320 mOsm/l, it increases the diuresis and can lead to dehydration, which may lead to systemic hypotension, ischaemia and hyperkalaemia. Prolonged use may also lead to osmotic flow reversal due to increased extravascular concentration, exacerbating intracranial oedema and elevating intracranial pressure (Bullock 1995; BTF 2007a; Dewey and Fletcher 2008).

The use of furosemide in patients with TBI is controversial. It was believed that this drug used in combination with mannitol could help increase diuresis and decrease hypertension. However, it has now been reported that the combination of furosemide and mannitol, or furosemide alone, did not result in any benefit to the patient, and may cause greater depletion of the intravascular volume, altering parameters such as heart rate, mean arterial pressure, central venous pressure, potassium, urea, haematocrit or base deficit (Sande and West 2010; DiFazio and Fletcher 2013; Dewey and Fletcher 2015).

3.5 Hypothermia

Therapeutic hypothermia is also a treatment method that can be used in patients who have suffered traumatic brain injury, since the development of several secondary lesions is temperature-dependent. The mechanism of action for hypothermia is based on a decrease of body temperature to 32–34 °C in order to reduce the release of excitotoxic amino acids and the production of proinflammatory cytokines as well as a decrease in excitatory signals that can result in cell death. As such, it would prevent necrosis and cell apoptosis, and reduce the formation of cerebral oedema and rupture of the blood-brain barrier (Hayes 2009; Sadaka and Veremakis 2012; McCarthy et al. 2013).

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There have been studies in humans that have also revealed the efficacy of therapeutic hypothermia as a neuroprotectant after intracranial haemorrhage, and it has been reported to decrease the formation of oedema (MacLellan et al. 2006; Fingas et al. 2007; Kawanishi et al. 2008).

A decrease in body temperature involves adverse effects. Studies in human adults and children have shown that there was no improvement in the neurological status of patients undergoing this treatment, but comparative studies have shown some efficacy in reducing intracranial pressure in children; therefore, this treatment may be considered (Clifton et al. 2001; Hutchison et al. 2008).

3.6 Hyperventilation

Hyperventilation is used to reduce intracranial pressure by reducing the partial pressure of CO_2 ($PaCO_2$), which consequently promotes brain vasoconstriction and subsequent reduction of brain blood volume. However, the use of this therapy is controversial as it can cause severe reduction of the cerebral circulation when values of $PaCO_2$ are smaller than 30–35 mm Hg. The patient should be ventilated to maintain $PaCO_2$ between 30–40 mm Hg, avoiding hypoventilation. Hyperventilation by itself can have deleterious effects related to cerebral vasculature dilatation in patients with high intracranial pressure, secondary to induced hypercapnia (White et al. 2001; Platt 2008; Dewey and Fletcher 2015).

3.7 Glucocorticoids

Currently, the use of glucocorticoids (GC) in the treatment of patients with cranioencephalic trauma is not recommended in human or veterinary medicine. Despite contributing to a reduction in cerebral oedema secondary to other causes, such as neoplasia, in patients with TBI, GCs lead to an increase in mortality. This was evaluated mainly by the use of methylprednisolone, which led to hyperglycaemia, immunosuppression, wound healing delay, gastric ulcers and acceleration of the catabolic state. It was further associated with a worsening of neuronal damage in the presence of ischaemia due to increased exposure to metabolic insults, and its association with inhibition of the remyelination of injured neurons was also noted (Platt 2008; Sande and West 2010; Gaitero 2011).

The functional mechanisms of corticosteroids are increasingly well understood and it is now known that these drugs are more efficacious in the treatment of the vasogenic type of oedema when compared to the cytotoxic one. Recent studies have shown that, despite the being effective *in vitro*, corticosteroids were not effective when used *in vivo.* Therefore, due to the lack of a complete understanding of the functional mechanisms of corticosteroids in cerebral metabolism in TBI and of a specific diagnostic test to determine the type of oedema present in such patients, their use is not yet recommended (Hoshide et al. 2016).

3.8 Anticonvulsants

Seizures are common in patients who have suffered TBI. They can be divided into three categories: immediate, occurring up to 24 hours after the trauma; early, from 24 hours to seven days after the trauma; and late, after seven days, depending on the severity of the lesion, the presence of cranial fractures, epidural, subdural, parenchymal haematoma and penetrating wounds (Bratton et al. 2007; Platt 2008; Sande and West 2010). The occurrence of seizures in patients with TBI should be treated aggressively as they lead to an elevation of intracranial pressure, worsening the patient's clinical condition. Diazepam is the drug of choice for the treatment of seizures, since it has a fast action and reliable efficacy at doses of 0.5 to 1.0 mg/kg which can be repeated in intervals of 5 to 10 minutes for three to four doses (Sande and West 2010; Lorenz et al. 2011).

Other drugs can be used in persistent convulsive episodes. Since diazepam (0.5 to 2 mg/kg) (Platt et al. 2016) does not have a prolonged effect, phenobarbital can be used. Phenobarbital is classified as a sedative and antiepileptic, it has antiapoptotic effects and does not promote changes in cerebral blood flow; therefore, it promotes neuroprotection. Phenobarbital has a latency period of 15 to 20 minutes (Neves et al. 2010) and can be used in doses of 2 to 3 mg/kg *i.v.* followed by a loading dose of 18 to 24 mg/kg parenterally, over a period of 24 to 48 hours. Recently, the use of levetiracetam has shown success in the treatment of emergency seizures due to its rapid effect and efficacy for up

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to 8 hours, with low sedative effect. The recommended doses of levetiracetam range from 20 to 60 mg/kg (Platt et al. 2016). The use of prophylactic anticonvulsants may also be indicated in patients with TBI even if there are no seizures, in order to avoid elevation of intracranial pressure. The recommended dose of phenobarbital is 2 mg/kg *i.m.* every 6 to 8 hours for three to six months after trauma, followed by gradual reduction of the dose down to complete cessation if there are no further seizures (Platt 2008).

Thiopental and propofol, both classified as anaesthetics, are also used. They exert anticonvulsant and neuroprotective effects similar to phenobarbital. Thiopental has a rapid action and is used at a dose of 10 mg/kg at 2.5% (Harman et al. 2012). Propofol should be slowly administered intravenously in small animals in a bolus dose of 1 to 6 mg/kg to control seizures, followed by a dose of 0.1–0.6 mg/kg/min (Thomas 2003). Studies in humans have confirmed the efficacy of prophylactic therapy with anticonvulsants following TBI, which reduces the risk of immediate seizures, but without effects on late convulsions. Therefore, treatment with anticonvulsants in patients with TBI who develop immediate or early seizures should always be used, and prophylactic therapy should be administered for seven days after the initial trauma (Dewey and Fletcher 2015).

3.9 Pain management

Pain management is crucial in the treatment of TBI, as it assists in controlling blood pressure, perfusion and cerebral oxygenation and ultimately in reducing intracranial pressure. Care should be taken to control analgesia, since the depression of these parameters with the elevation of intracranial pressure may result in the worsening of secondary lesions. Opioids are the drugs of choice in the treatment of TBI pain, since their effects are easily reversible and they do not have adverse cardiovascular effects, making them safer. However, one should always take into account their side effects, which include bradycardia, respiratory depression and hypotension, especially when used in high doses (BTF 2007b; Roberts et al. 2012).

The use of morphine should be avoided because it causes emesis as a side effect, which could lead to an elevation in intracranial pressure. The use of fentanyl, a potent analgesic with short duration and fast action, is preferable. It is used in continuous infusion at a dose of 2–5 µg/kg/h or cutaneous adhesives supplying 2–5 µg/kg. Caution should be taken because its use may lead to a slight increase in intracranial pressure (Raslan and Bhardwaj 2007). If there are side effects, naloxone can be used as an antagonist, reversing the effect of this drug (Armitage-Chan et al. 2006; Sande and West 2010; Opperman 2014).

The opioid agonist-antagonist butorphanol and the partial agonist buprenorphine may be used in the treatment of mild to moderate pain; they cause minor respiratory and cardiovascular changes and are preferably used in cases where the patient already presents with respiratory depression. However, side effects are more difficult to reverse using naloxone compared to opioids (Armitage-Chan et al. 2006; BTF 2007c; Sande and West 2010; Opperman 2014).

3.10 Decompressive surgery

Decompressive craniectomy consists of a surgical technique where a bone flap is removed to be housed for a period in the abdominal subcutaneous tissue, kept in a bone bank or prepared for later cranioplasty with heterologous materials. Durotomy and expansion duroplasty techniques may be associated to reduce ICP, using an autologousaponeurotic galea graft. Decompressive craniectomy promotes a decrease in intracranial pressure and accommodation of the tumefied brain, preventing the onset of intracranial brain hernias and is indicated for patients with cranial fractures, depressed cranial fractures with neurological impairment and recovery of potentially contaminated bone fragments or foreign material housed in the cerebral parenchyma. According to the European Brain Injury Consortium (EBIC) and the Brain Trauma Foundation guidelines, decompressive craniectomy is classified as a second level for the treatment of refractory intracranial hypertension (BTF 2007c; Hutchinson et al. 2007; Cooper et al. 2011).

In general, surgical intervention is well defined in human head-trauma management, whereas it has played a relatively minor role for canines and felines. It is believed that for these animals, significant intracranial haemorrhage is rare, although,

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similar to humans, they may experience intracranial haemorrhage manageable via surgery. The increasing availability of CT as a diagnostic method might lead to surgery assuming a larger role in the treatment of traumatic brain injury (da Costa and Dewey 2015).

The aim of surgery is to increase intracranial volume, improve brain compliance, reduce intracranial pressure and elevate cerebral perfusion pressure, thereby elevating cerebral blood flow and cerebral microvascular perfusion. When bone fragments are present and the skull sinking is greater than its thickness, it is recommended to perform decompression via fracture reduction or removal of bone fragments. In the case of acute extra-axial haematomas, craniotomy can be performed. Caution should be taken in the case of excessive bleeding when haematoma is secondary to a venous sinus fracture (Seim 2007; Platt 2008; Siqueira et al. 2013).

However, surgical decompression is controversial, since studies show that decompressive craniectomy may worsen the patient's clinical condition due to increased cerebral oedema and may be associated with cerebral hyperaemia due to an increase in cerebral perfusion pressure after surgery, a decrease in reactivity of cerebral vascular pressure and cerebral inflammation. In addition, decompressive craniectomy in the veterinary patient should be approached with caution since there is neurological impairment even with aggressive drug therapy. Studies have revealed this neurological impairment when comparing patients that underwent the surgical procedure and those who only received clinical treatment; there was a worsening in the modified Glasgow coma scale in those submitted to decompressive craniectomy (Timofeev et al. 2008; Bao et al. 2010; Dewey and Fletcher 2015).

4. Prognosis

Many prognostic factors have been identified in human medicine and have been extrapolated to dogs and cats. The most important ones include age, cause of injury, Glasgow coma scale, neurological examination parameters, presence of subarachnoid haemorrhage and laboratory parameters such as glycaemia and prothrombin time, blood pressure and results found in CT exams. The most common sequelae include coagulopathies, pneumonia, sepsis, diabetes insipidus and posttraumatic epilepsy, behavioural changes, visual deficits and late hydrocephalus. The prognosis in TBI varies from reserved to bad, although dogs and cats have a remarkable ability to regenerate brain tissue (Murray et al. 2007; Sande and West 2010).

Traumatic brain injury occurs frequently in dogs and cats with a high mortality rate, mainly due to the secondary lesions that occur within minutes of the injury. Many therapeutic measures are proposed; however, most are inconsistent as they lack randomised clinical trials that proving their efficacy.

The relevant literature reveals some disagreements regarding the treatment of TBI; however, the authors of published papers are unanimous among that treatment should be multimodal, and there is an intense search to discover new pathways for its treatment. It is clear that the management of TBI should be directed towards restoring cerebral perfusion pressure, thus maintaining blood flow and oxygenation, avoiding an increase in intracranial pressure and minimising elevations in the cerebral metabolic rate.

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Received: February 9, 2017
Accepted after corrections: June 1, 2018