Updates in the Management of the Small Animal Patient with Neurologic Trauma

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Neurologic trauma, encompassing traumatic brain injury (TBI) and acute spinal cord injury (SCI), is a cause of significant morbidity and mortality in veterinary patients. In one recent retrospective study evaluating blunt trauma in dogs, a diagnosis of TBI was made in 25\% of cases and was associated with increased mortality.\textsuperscript{1} Acute SCIs occurring secondary to trauma (including vertebral fracture or luxation [VFL], traumatic intervertebral disk herniation, spinal cord parenchymal contusions, and extra-axial hemorrhage) are also common, with an estimated incidence rate of 14\% in cats and 9\% in dogs based on the information from single-center retrospective studies.\textsuperscript{2,3} The causes of neurologic trauma in dogs and cats include motor vehicular trauma, falls, crush injuries, bite wounds, missile injuries (e.g., gunshot wounds), and either accidental or purposeful human-inflicted trauma.\textsuperscript{4–7} Essential to the management of TBI and SCI is a thorough understanding of the pathophysiology of the primary and secondary injury that occurs following trauma.\textsuperscript{8} This article reviews the

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pathophysiology of this primary and secondary injury, as well as recommendations regarding clinical assessment, diagnostics, pharmacologic and nonpharmacologic therapy, and prognosis.

**MANAGEMENT GOALS**

Damage to nervous tissue can be divided into primary and secondary injury. Primary injury occurs immediately after trauma and is the direct result of traumatic impact. Secondary injury is often referred to as delayed injury, but usually begins within minutes of injury and can last several days to weeks afterward. These categories may seem artificial at first, but are important when considering management.

Most TBI therapies are aimed at minimizing the effects of secondary injury. Because instability contributes to exacerbation of primary injury, depending on the type, management of acute SCI may include surgical therapy directed at stabilization to prevent further primary injury in addition to therapies directed at minimizing the effects of secondary injury.

**Primary Injury**

Primary injury associated with TBI and SCI involves the physical disruption of intracranial structures (eg, TBI) and the spinal cord, vertebrae, and supporting structures (eg, SCI) that occurs at the time of impact. Primary injury is broadly classified as focal or diffuse depending on the extent of injury, and more specifically can be defined based on the location and type of injury. The principal mechanical forces involved in neurologic trauma include concussion (eg, acceleration and deceleration), compression, shear, laceration, distraction, and contusion. Primary injuries associated with TBI include epidural hematomas, subdural hematomas, subarachnoid hemorrhage, cortical contusions/hematomas, and traumatic axonal injury. Primary SCI includes VFL, traumatic intervertebral disc herniation, intraparenchymal contusion, and extraxial hemorrhage.

**Secondary Injury**

Box 1 summarizes the local factors contributing to secondary injury in neurologic trauma. In addition, multiple systemic factors can potentiate secondary injury, most importantly hypoxia and hypotension but also hypercapnia, hypocapnia, hyperglycemia, hypoglycemia, acid-base disturbances, electrolyte abnormalities, hyperthermia, and systemic inflammation. Other intracranial factors can also exacerbate secondary injury in TBI, including intracranial hypertension, edema, compromise of the blood-brain barrier (BBB), vasospasm, hemorrhage, infection, mass effects, and seizure activity.

Secondary injury is potentiated by compromise of perfusion. Cerebral perfusion pressure (CPP) is defined as the net pressure facilitating blood flow to the brain, and is the difference between the mean arterial blood pressure (MAP) and intracranial pressure (ICP): CPP = MAP – ICP. Similarly, spinal cord perfusion pressure (SCPP) is the difference between MAP and cerebrospinal fluid pressure (CSFP): SCPP = MAP – CSFP.

The Monroe-Kellie doctrine states that the cranial vault is a rigid, defined space that has a fixed volume with contributions from the brain parenchyma, cerebrospinal fluid (CSF), blood, and mass lesions (if present). An increase in the volume of any of these will result in a compensatory decrease in 1 or more of the others (defined as intracranial compliance; mainly reliant on changes in CSF or blood volumes), without which a pathologic increase in ICP will occur. With TBI the compensatory capacity of
intracranial compliance can be overwhelmed, and intracranial hypertension may occur. Increases in ICP combined with decreases in MAP, a finding that is common in trauma patients, can result in decreases in CPP. In addition, compromise of autorregulatory mechanisms (eg, vasodilation/constriction of cerebral arterioles that maintain constant cerebral and spinal cord blood flow over a wide range of MAP ([0–150 mm Hg]) results in a more linear association between blood flow and MAP, leading to a greater risk of hypoperfusion or hyperemia.11

Severe, acute intracranial hypertension may result in the Cushing reflex or central nervous system (CNS) ischemic response. Decreased cerebral blood flow results in elevations in carbon dioxide (CO₂) levels sensed locally at the vasomotor center, causing a dramatic increase in sympathetic tone, ultimately leading to systemic vasoconstriction and increased cardiac output.23 Increases in MAP stimulate baroreceptors in the aortic and carotid sinuses, resulting in a reflex sinus bradycardia. This response signifies potentially life-threatening intracranial hypertension and should be treated immediately.4,7,17

DIAGNOSTIC EVALUATION
Systemic Assessment

Initial triage assessment of the trauma patient should focus on global patient stability with special emphasis on the respiratory and cardiovascular systems. In patients with neurotrauma, this is perhaps even more important because hypotension, hypoxemia, and changes in ventilation contribute to secondary injury and worsen outcome.

Neurologic Assessment

The initial neurologic examination should occur before administration of any analgesic therapy to allow adequate assessment of the neurologic system. Initial neurologic examination should include an evaluation of mentation, cranial nerve reflexes, ambulatory status, presence of voluntary motor function (assessed only in recumbency in the nonambulatory patient with potential VFL), presence of superficial pain perception in the patient who does not demonstrate voluntary motor function, presence of deep pain sensation in the patient who does not demonstrate intact superficial pain perception, spinal reflexes, panniculus reflex, anal tone, and perineal reflex. If the patient is ambulatory and the clinician is not suspicious of a VFL, assessment of gait and proprioceptive function can also occur. Gentle palpation of the spinal column should be done in all patients presenting with possible acute SCI to localize regions of malalignment (eg, “step” fracture), instability, discomfort, or crepitus. When performing a neurologic assessment, it is important that the patient has been adequately resuscitated, as shock can affect neurologic status. In addition, it is important that a thorough recumbent orthopedic examination also be performed to rule out orthopedic injury as a potential cause for apparent neurologic signs.13,15

Whenever SCI secondary to VFL is suspected in the nonambulatory patient, minimal movement of the patient should occur. The patient should be immobilized and secured to a backboard until definitive assessment for fractures and luxations can occur.13,15

Patients should be neurolocalized and graded based on severity of signs. The Modified Glasgow Coma Scale (MGCS) has been validated in dogs, and is useful in the assessment of TBI patients, as it provides a means of more objectively determining improvement or progression of clinical signs. It also yields prognostic information (Box 2).24,25 One retrospective study showed that the MGCS correlated well with the probability of survival in the first 48 hours after TBI in dogs.25 Repeated neurologic
**Box 1**
**Mechanisms of secondary injury**

**Secondary Injury**

*Glutamate accumulation*
- Occurs secondary to:
  - Adenosine triphosphate (ATP) depletion
  - Neuronal cell injury
  - Positive feedback
  - Decreased conversion
  - Potentiated by low interstitial magnesium
- Results in:
  - Loss of ionic gradients
  - Excitotoxicity
  - Generation of free radical oxygen species

*Influx of sodium into neuronal cells*
- Occurs secondary to:
  - Glutamate accumulation
- Results in:
  - Cytotoxic edema

*Influx of calcium into neuronal cells*
- Occurs secondary to:
  - Glutamate accumulation
  - Primary injury
- Results in:
  - Cytotoxic edema
  - Neuronal cell destruction through activation of proteases, lipases and endonucleases
  - Reactive oxygen species production through calpain activation
  - Inflammatory mediator release
  - Mitochondrial dysfunction and ATP depletion

*Free radical production*
- Occurs secondary to:
  - Glutamate accumulation
  - Inflammatory mediator release
  - Increased cytosolic calcium concentrations
  - Ischemia-reperfusion injury
- Results in:
  - Neuronal cell destruction

*Inflammatory mediator release*
- Occurs secondary to:
  - Primary injury
Neuronal cell destruction with secondary injury

- Results in:
  - Activation of nitric oxide with alterations in blood flow and vascular permeability
  - Inflammatory cell influx
  - Coagulation cascade activation and thrombosis

**Loss of autoregulation**

- Occurs secondary to:
  - Primary injury

- Results in:
  - Ischemia

All mechanisms contribute to neuronal cell death

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**Box 2**

**Modified Glasgow Coma Scale**

**Level of Consciousness**

6. Occasional periods of alertness and responsive to environment
5. Depression or delirium, capable of responding but response may be inappropriate
4. Semicomatose, responsive to visual stimuli
3. Semicomatose, responsive to auditory stimuli
2. Semicomatose, responsive only to repeated noxious stimuli
1. Comatose, unresponsive to repeated noxious stimuli

**Brainstem Reflexes**

6. Normal pupillary light reflexes and oculocephalic reflexes
5. Slow pupillary light reflexes and normal to reduced oculocephalic reflexes
4. Bilateral unresponsive miosis with normal to reduced oculocephalic reflexes
3. Pinpoint pupils with reduced to absent oculocephalic reflexes
2. Unilateral, unresponsive mydriasis with reduced to absent oculocephalic reflexes
1. Bilateral, unresponsive mydriasis with reduced to absent oculocephalic reflexes

**Motor activity**

6. Normal gait, normal spinal reflexes
5. Hemiparesis, tetraparesis, or decerebrate activity
4. Recumbent, intermittent extensor rigidity
3. Recumbent, constant extensor rigidity
2. Recumbent, constant extensor rigidity with opisthotonus
1. Recumbent, hypotonia of muscles, depressed or absent spinal reflexes
assessment is recommended every 30 to 60 minutes after initial presentation to assess clinical response to therapy or progression of clinical signs. There are currently 3 validated scoring systems available for assessing the severity of deficits associated with SCI: the Modified Frankel Score, the 14-Point Motor Score, and the Texas Spinal Cord Injury Score.26,27

Brachial plexus injuries should be suspected if a patient has decreased reflexes in only one of the forelimbs, Horner syndrome on the affected side, and decreased panniculus reflex on the affected side.13 The presence of spinal shock may affect neurolocalization in patients with acute SCI. Spinal shock leads to deficits in segmental spinal reflexes caudal to a lesion, even though the reflex arcs remain physically intact, causing flaccid paralysis, due to a sudden interruption in descending supraspinal input that occurs with acute SCI. Recovery from spinal shock in humans is protracted, but in dogs and cats occurs much more rapidly, typically within 12 to 24 hours.28

**Imaging**

*Extra-CNS assessment*

As with any trauma patient, imaging should include thoracic radiographs to rule out pulmonary contusions, pneumothorax, and other chest or pulmonary trauma, as well as imaging of the abdomen. Ideally, additional diagnostics such as ultrasonographic imaging via focused assessment with sonography for trauma can also be performed to rule out organ fracture and peritoneal effusion (eg, hemoperitoneum, uroperitoneum, septic peritonitis).29,30

*Intracranial and spinal assessment*

Intracranial imaging for the TBI small animal patient is indicated in patients who fail to respond to aggressive medical management, patients who deteriorate after an initial response to medical therapy, and/or those patients with focal or asymmetric neurologic signs. Computed tomography (CT) is the modality of choice for characterization of TBI in the acute setting, as it is quick, relatively inexpensive, and has excellent ability to identify extra-axial hemorrhage (eg, epidural, subdural, and subarachnoid/intraventricular hemorrhage), intra-axial hemorrhage (eg, cortical contusion, intraparenchymal hematoma, and traumatic axonal injury), cerebral swelling, and cerebral herniation.9–11 Beyond the acute setting, magnetic resonance imaging (MRI) is recommended when patients continue to be nonresponsive to medical therapy or deteriorate with continued aggressive management despite having normal CT scans.10,11

Although plain radiography can yield important information regarding SCI in small animal patients, it has been shown to have relatively low sensitivity for detecting vertebral fractures (72%) and subluxations (77.5%) in dogs.31 Orthogonal radiographs (ie, both views obtained in lateral recumbency using the horizontal beam technique) should be obtained if more advanced imaging is unavailable. The entire spine should be imaged, as approximately 20% of patients with spinal trauma have multiple VFLs.32 Absence of VFLs on radiographs should not be used to definitively exclude their presence. Radiographic signs associated with intervertebral disk herniation include narrowing of the disk space, mineralized disk material, narrowing of the articular facets, and narrowing or increased opacity of the intervertebral foramen.33,34 These signs have relatively low accuracy (51%–61%), sensitivity (64%–69%), and positive predictive value (63%–71%) in diagnosing disk herniation.35 In addition, other SCIs can occur with trauma that may not be evident with radiography alone.

CT is the imaging modality of choice for bone, and therefore is recommended in the patient whose clinical signs are suggestive of an unstable VFL. CT has been documented to have sensitivity of up to 100% in some human studies for the diagnosis
of VFLs. Myelography and CT can be combined, and yields the highest sensitivity for detecting intervertebral disk herniation sites, though CT alone still maintains relatively good sensitivity. Although CT requires sedation or general anesthesia, modern CT scanners are very quick, making this a feasible imaging approach for the polytrauma patient. Whole-body CT scans can often be obtained in less than a minute and allow assessment of the skull, brain, spine, thorax, and abdomen.

Myelography involves injecting contrast into the subarachnoid space and identifying attenuation of the ventral, dorsal, or lateral contrast columns at sites of extradural compression. Myelography provides more information than plain radiography regarding the site of intervertebral disk herniation. Studies have shown agreement between myelographic and surgical findings of approximately 81% to 98%, with accuracy for lateralization of the lesion being approximately 53% to 100%.34–37 However, myelography provides little additional information regarding presence of VFLs or intraparenchymal injury. Myelography requires general anesthesia and also carries risks associated with contrast administration, including postprocedure seizures.38,39

MRI is considered the superior imaging modality for soft tissue including the spinal cord parenchyma, intervertebral disks, and nerve roots. However, it provides relatively poor detail of bony structures and, therefore, is not the modality of choice when pursuing further imaging for VFLs.40 This modality is more expensive than other techniques and requires longer periods of anesthesia. At the authors’ institution it is typically used when other techniques (eg, CT) fail to reveal a cause for neurologic dysfunction in the traumatic SCI patient.

PHARMACOLOGIC STRATEGIES

Systemic Therapy

Oxygen therapy
Oxygen should be supplemented if needed to maintain normoxemia (oxygen partial pressure \[PaO_2\] = 80–100 mm Hg and pulse oxygen saturation \[SpO_2\] = 94%–98%), but should be titrated to avoid hyperoxemia, which could worsen reperfusion injury.7 Methods for providing oxygen include flow-by mask, nasal or nasopharyngeal cannulation, oxygen cages or tents, and endotracheal administration.41 Flow-by mask administration is typically recommended during initial assessment and resuscitation until oxygenation monitoring can be initiated. Nasal or nasopharyngeal cannulation has the benefit of ensuring high concentrations of inspired oxygen, but nasal stimulation can induce sneezing, which can lead to increases in ICP. Because of reduced levels of consciousness, most TBI patients tolerate nasal oxygen quite well. Oxygen cages also can provide relatively high levels of inspired oxygen, but unfortunately minimize access to the critically ill patient.42 Each patient should be evaluated and the best modality for oxygen administration determined for the individual. If adequate oxygenation cannot be maintained with high fractional oxygen concentrations (\[FiO_2\]) greater than 60%, mechanical ventilation is indicated.43

Intravenous fluid therapy
Controversy exists in veterinary medicine regarding the best choice of fluid for resuscitation in the neurotrauma patient. Options for fluid resuscitation include isotonic crystalloids, hypertonic solutions, artificial colloidal solutions, and blood products. Concern exists particularly in TBI management regarding the injured brain’s capacity to protect against increases in cerebral edema when faced with fluids containing large amounts of free water caused by disruption of cellular tight junctions and subsequent influxes of ions and larger, colloid-sized molecules with secondary osmotic pull.4 It is therefore recommended that isotonic fluids containing the least amount of free water (eg, 0.9%
NaCl) be administered, barring significant sodium derangements already present on presentation. Because fluid shifts between the interstitial and intracellular compartments of the brain are predominantly dictated by osmolality as opposed to plasma oncotic pressure, colloidal solutions have not demonstrated any significant benefit over crystalloid therapy. However, owing to rapid redistribution of crystalloids after administration, a combination of colloidal therapy with crystalloid therapy (either isotonic or hypertonic) can be considered to provide longer-lasting volume resuscitation.

Hypertonic saline (HTS) has several potential benefits in the neurologic trauma patient (particularly the TBI patient), including rapidly increasing intravascular volume, increasing cardiac output, improving regional cerebral and spinal cord blood flow by dehydrating cerebrovascular endothelial cells, increasing vessel diameter, decreasing ICP, and enhancing cerebral oxygen delivery. It is important that the concentration of HTS being used is noted, as this will affect the dosing of the solution. HTS should be used only in euhydrated patients without significant sodium derangements. In addition, it is imperative that HTS be followed by crystalloid therapy to maintain adequate tissue hydration.

Anemic patients should be treated with packed red blood cells or whole blood to maintain adequate arterial oxygen content and oxygen delivery to damaged nervous tissue. Transfusion goals include normalization of perfusion parameters (including central venous oxygen saturation >70%). Fresh frozen plasma should be administered to the coagulopathic patient. Those patients that do not respond to fluid resuscitation warrant vasopressor support. After initial fluid resuscitation, fluid therapy should be continued to account for maintenance needs, deficits, and any ongoing losses. Recommended initial bolus dosing of intravenous fluids are listed in Table 1.

**Pain management**

Analgesic therapy is essential in the management of the neurotrauma patient. The degree of analgesia and sedation must be balanced with preservation of blood pressure and ventilatory status, as depression of each of these parameters can contribute to secondary injury, and if possible should not impede reassessment of neurologic status. Adequate analgesia in the TBI patient avoids transient increases in ICP caused by pain and agitation, which can lead to increased cerebral metabolic rate and, consequently, cerebral blood flow and volume.

Opioids are the analgesic drugs of choice in critical care medicine, because of their ease of reversal and relative safety when titrated to effect. Several studies suggest that bolus infusion of opioids should be avoided, and constant-rate infusions (CRIs) are preferred. Because of the ease of reversal, it is recommended that full agonist opioids be used.

Ketamine noncompetitively inhibits the N-methyl-D-aspartate (NMDA) receptor; therefore, this agent may have neuroprotective properties against ischemic and glutamate-induced injury in addition to its cardiovascular and respiratory-sparing properties. Recent studies have failed to demonstrate that ketamine results in the ICP increases typically reported in the older literature. However, it has been shown to increase cerebral oxygen consumption, possibly through inhibition of the \( \gamma \)-aminobutyric acid (GABA) receptor. Therefore, administration with a GABA agonist (eg, propofol) potentially could decrease these negative effects.

Medetomidine, an \( \alpha \)-agonist, has been documented to have no effect on ICP in anesthetized dogs. Caution must be exercised in using this class of drugs for their analgesic or sedative properties, as they can cause clinically significant reductions in heart rate and cardiac output, thereby affecting CNS perfusion. Table 2 lists the recommended analgesics and their respective doses.
Intracranial hypertension has consistently been associated with poor outcomes in patients with TBI. Hyperosmolar therapy has been the cornerstone of managing intracranial hypertension since the early twentieth century when HTS and glucose solutions were documented to decrease CSF pressure in cats. The brain is composed

### Table 1

<table>
<thead>
<tr>
<th>Fluid Type</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isotonic crystalloid (0.9% NaCl preferred)</td>
<td>20–30 mL/kg dogs; 10–20 mL/kg cats Administered over 15–20 min Reassess after</td>
</tr>
<tr>
<td>Synthetic colloid (eg, 6% hydroxyethylstarch)</td>
<td>5–10 mL/kg Administered over 15–20 min Reassess after</td>
</tr>
<tr>
<td>7.5% NaCl</td>
<td>4 mL/kg Administered over 15–20 min Reassess after</td>
</tr>
<tr>
<td>3% NaCl</td>
<td>5.4 mL/kg Administered over 15–20 min Reassess after Always follow with crystalloid therapy</td>
</tr>
<tr>
<td>1:2 Ratio of 23.4% NaCl and 6% hydroxyethylstarch or other synthetic colloid</td>
<td>4 mL/kg Administered over 15–20 min Reassess after Always follow with crystalloid therapy</td>
</tr>
<tr>
<td>Packed red blood cells</td>
<td>~10–15 mL/kg Administer over less than 4 h/unit Target normalization of perfusion parameters and packed cell volume (PCV) = 25%–30%</td>
</tr>
<tr>
<td>Whole blood</td>
<td>~20–30 mL/kg Administer within 4 h/unit Target normalization of perfusion parameters and PCV = 25%–30%</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>10–15 mL/kg Administer within 4 h/unit Target normalization of coagulation times</td>
</tr>
</tbody>
</table>

### Pharmacologic Strategies Specific for TBI

**Hyperosmolar therapy**

Intracranial hypertension has consistently been associated with poor outcomes in patients with TBI. Hyperosmolar therapy has been the cornerstone of managing intracranial hypertension since the early twentieth century when HTS and glucose solutions were documented to decrease CSF pressure in cats. The brain is composed

### Table 2

<table>
<thead>
<tr>
<th>Analgesic</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>Dogs: 2 µg/kg, then constant-rate infusion (CRI) at 2–5 µg/kg/h Cats: 1 µg/kg, then CRI at 1–2 µg/kg/h</td>
</tr>
<tr>
<td>Morphine</td>
<td>Dogs: 0.15–0.5 mg/kg slow, then CRI at 0.1–1 mg/kg/h</td>
</tr>
<tr>
<td>Ketamine</td>
<td>0.1–1 mg/kg, then CRI at 2–10 µg/kg/min</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Dogs: 1–2 mg/kg, then CRI at 25–80 µg/kg/min</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>0.5–1 µg/kg/h</td>
</tr>
</tbody>
</table>
of approximately 80% water, making its volume very responsive to changes in water content. An osmotic agent is only effective if the BBB is impermeable to it. Sodium and mannitol have near perfect exclusion by the BBB, making HTS and mannitol extremely effective for addressing intracranial hypertension. Hyperosmolar therapy in TBI predominantly affects normal, rather than injured, brain tissue. Mannitol is a sugar alcohol that is not significantly metabolized and is excreted unchanged in the urine after intravenous infusion. It is recommended as a first-line treatment for intracranial hypertension. Table 3 summarizes mannitol’s mechanisms of action, recommended dosing, and side effects. Mannitol is not recommended for prophylactic use in patients with TBI unless there is concern for elevations in ICP, because its effectiveness is related to the degree of intracranial hypertension and its associated response decreases as the cumulative dose increases (ie, it may be less effective when actually necessary). Mannitol administration should always be followed by isotonic crystalloid and/or colloid therapy to avoid hypovolemia caused by its diuretic effect, and serum osmolarity should ideally be measured, if possible, when repeated doses are administered.

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>Mannitol</th>
<th>Hypertonic Saline</th>
</tr>
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<tbody>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Increases osmotic gradient across BBB</td>
<td>Increases osmotic gradient across BBB</td>
</tr>
<tr>
<td></td>
<td>Plasma expansion with decreased blood viscosity</td>
<td>Volume expansion</td>
</tr>
<tr>
<td></td>
<td>Improves brain oxygen delivery and autoregulation</td>
<td>Increases cardiac output and blood pressure</td>
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<tr>
<td></td>
<td>Results in cerebral vasoconstriction, decreasing cerebral blood volume and ICP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Free radical scavenger</td>
<td></td>
</tr>
<tr>
<td><strong>Recommended dose</strong></td>
<td>0.5–1.0 g/kg slow over 15–20 min</td>
<td>7.5% NaCl: 4 mL/kg</td>
</tr>
<tr>
<td></td>
<td>Effects begin within minutes, peak within 15–120 min, duration 1–5 h</td>
<td>3% NaCl: 5.4 mL/kg</td>
</tr>
<tr>
<td></td>
<td>No benefit of CRI over boluses</td>
<td>1:2 ratio 23.4% NaCl to 6%, Hetastarch: 4 mL/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Administered over 15–20 min</td>
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<tr>
<td></td>
<td></td>
<td>Reassess after</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Always follow with crystalloid therapy</td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>Volume depletion</td>
<td>Electrolyte abnormalities</td>
</tr>
<tr>
<td></td>
<td>Electrolyte abnormalities (hyponatremia [pseudo-], hypernatremia, hypokalemia)</td>
<td>(hypernatremia, hyperchloremia)</td>
</tr>
<tr>
<td></td>
<td>Acid-base derangements (eg, metabolic acidosis)</td>
<td>Acid-base derangements (eg, metabolic acidosis)</td>
</tr>
<tr>
<td></td>
<td>Congestive heart failure</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td></td>
<td>Acute kidney injury (osmolality &gt;320 mOsm/L)</td>
<td>Acute kidney injury (less common than with mannitol)</td>
</tr>
<tr>
<td><strong>Relative contraindications</strong></td>
<td>Hypovolemia</td>
<td>Significant sodium derangements</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dehydration</td>
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*Abbreviations: BBB, blood-brain barrier; CRI, constant-rate infusion; ICP, intracranial pressure.*
Hypertonic saline therapy affords similar osmotic benefits as mannitol therapy, but is a less potent diuretic. **Table 3** summarizes HTS’s mechanisms of action, recommended dosing, adverse effects, and relative contraindications.63,66 It is generally recommended that sodium concentrations be maintained at less than 160 mEq/L, although concentrations of up to 180 mEq/L have been reported in humans treated with hypertonic saline with no complications.67

There is no evidence that mannitol is superior to HTS in the treatment of intracranial hypertension or vice versa. The small number of studies available have shown conflicting results.68–71 It is likely that HTS is preferable in hypovolemic patients, but in euvolemic patients, either is reasonable. When patients do not respond to treatment with one agent, the alternative should be considered.

Administration of furosemide alone or concurrently with mannitol to treat intracranial hypertension has not been shown to have any additional benefit and increases the risk of volume depletion.72 Therefore, its use is not recommended.

**Corticosteroids**
Corticosteroids were previously advocated for in the treatment of TBI patients on the basis that corticosteroids decreased cerebral edema. Ground-breaking evidence from the CRASH trials showed that high-dose methylprednisolone was associated with an increase in mortality at 2 weeks and 6 months after injury.73,74 Corticosteroids are therefore no longer recommended in the treatment of TBI patients.

**Anticonvulsant therapy**
Posttraumatic seizures are classified as immediate (occurring within 24 hours of injury), early (occurring 24 hours to 7 days after injury), or late (occurring more than 7 days after injury).62 Seizures increase secondary brain injury by increasing cerebral metabolic demands, increasing ICP, and leading to the release of excessive neurotransmitters. A recent Cochrane meta-analysis concluded that prophylactic antiepileptic drugs are effective in reducing early seizures, but there is no evidence that they are effective in preventing late-onset seizures. Therefore, prophylactic antiepileptic drugs are recommended for 7 days post-TBI in humans.75 There are few data in veterinary medicine, but if seizures develop, aggressive antiepileptic drug (AED) therapy is indicated to reduce secondary brain injury. The incidence of posttraumatic seizures in small animals is not well documented, but seizures are known to occur. At present, there are no clear recommendations for prophylactic AED therapy in veterinary medicine. If risk factors for seizures are present (eg, penetrating head wounds, depressed skull fractures, and so forth), it is reasonable to consider prophylactic AED therapy for the first 7 days after injury, based on human recommendations. The duration of AED therapy is debatable. Should seizures occur, benzodiazepines should be used as a first-line treatment to stop seizure activity.76 A variety of AEDs for continued seizure control are available for use in dogs and cats, and these are listed in **Table 4**. At the authors’ institution, levetiracetam is frequently used for its rapid onset of action, minimal side effects, and low toxicity potential.

**Barbiturate therapy**
Barbiturates are considered secondary therapy for the treatment of refractory intracranial hypertension in people, as high-dose therapy can control ICP when other medical and surgical therapies have failed. However, no outcome benefit has been documented.52 The neuroprotective effects of barbiturates are related to their ability to cause cerebral vasoconstriction, decrease cerebral metabolism, reduce ICP, decrease excitotoxicity, and decrease free radical–mediated injury.77 Barbiturates also have anticonvulsant properties. Complications associated with the use of barbiturates
include cardiovascular and respiratory depression, with potentially clinically significant hypotension (and associated decreases in CPP) and hypoventilation. The most widely used barbiturate for TBI is pentobarbital. Barbiturate coma (induced with drugs such as phenobarbital or other sedatives) was recently described in association with therapeutic hypothermia (TH) in a dog with TBI and refractory seizure activity. Patients in which barbiturate therapy is instituted must be monitored closely for hypoventilation, and may require mechanical ventilation.

**Novel therapies**

New therapies targeting excitotoxicity and production of reactive oxygen species are currently being investigated in human medicine, but none have been examined in veterinary practice to date. A recent randomized controlled trial of amantadine in vegetative or minimally conscious humans recovering from TBI showed significantly faster functional recovery over a 4-week period in treated patients. In the near future, more options specifically targeting secondary injury may become available to veterinary practitioners.
**Pharmacologic Strategies Specific for Acute SCI**

**Corticosteroids**

The use of corticosteroids in the treatment of acute SCI in humans and animals remains controversial despite extensive clinical research. Proposed mechanisms supporting the use of corticosteroids in SCI include free radical scavenging, anti-inflammatory effects, and improved regional blood flow.\textsuperscript{13,15} Much of the clinical and experimental research on corticosteroid therapy in SCI has focused on methylprednisolone sodium succinate (MPSS). The main neuroprotective property of MPSS appears to be its free radical–scavenging ability. Other corticosteroids (eg, prednisone and dexamethasone) lack this property, and are unlikely to have any beneficial effect in the treatment of secondary SCI.\textsuperscript{80} Specific evaluation of dexamethasone therapy in dogs has also failed to reveal any benefit in SCI, either experimentally or clinically.\textsuperscript{81,82} A series of 3 human clinical trials (National Acute Spinal Cord Injury Studies [NASCIS] I–III) provide the majority of primary evidence relating to the use of MPSS for the treatment of acute SCI.\textsuperscript{83–85} None of these studies convincingly demonstrated a benefit of steroids in improving motor function scores, as most of the statistically significant results were based on post hoc subgroup analyses.\textsuperscript{86} An experimental study in dogs comparing urgent surgical decompression with MPSS for the treatment of experimentally induced SCI showed that surgical decompression 6 hours after injury (with or without MPSS) resulted in better neurologic outcomes than treatment with MPSS alone.\textsuperscript{87} Another experimental dog study showed no improvement in outcome with MPSS administration.\textsuperscript{88} There are no published clinical placebo-controlled trials evaluating the efficacy of MPSS in the treatment of SCI in dogs, although there is currently one under way.\textsuperscript{16} Given the potential for significant adverse side effects, such as gastrointestinal ulceration, immunosuppression, and compromise of renal perfusion in hypovolemic patients, the routine administration of corticosteroids (including MPSS) is not recommended.\textsuperscript{13} 

**Box 3** summarizes additional pharmacologic therapies directed at minimizing secondary injury in acute SCI that have been investigated.\textsuperscript{89–101}

**NONPHARMACOLOGIC STRATEGIES**

**Systemic Therapy**

**Airway management and ventilation**

The upper airway should be directly examined and suctioned if necessary when a neurotrauma patient is initially presented. If the airway is deemed nonpatent or if the patient is unable to control its airway, immediate endotracheal intubation or emergency tracheostomy (if unable to intubate) is indicated.\textsuperscript{7} Carbon dioxide has profound effects on cerebral and spinal cord blood flow and blood volume.\textsuperscript{102} Both hypoventilation and hyperventilation should be avoided in neurotrauma patients, and close monitoring of CO\textsubscript{2} using end-tidal CO\textsubscript{2} (ETCO\textsubscript{2}) monitors or blood-gas analysis is warranted. Normal partial pressure of carbon dioxide (P\textsubscript{CO}\textsubscript{2}) (venous, 40–45 mm Hg; arterial, 35–40 mm Hg) should be targeted in all cases.\textsuperscript{62} Titration of analgesic medication, positioning in sternal recumbency, and ensuring that the airway is unobstructed can help address ventilation issues, but if these interventions are unsuccessful, endotracheal intubation and mechanical ventilation are indicated. Those patients at risk of cerebral herniation or that have experienced significant neurologic decompensation can be hyperventilated for short periods of time. However, the targets of short-term hyperventilation should be conservative (ETCO\textsubscript{2} = 30–35 mm Hg) to prevent excessive cerebral vasoconstriction and ischemic brain injury. Studies evaluating prophylactic hyperventilation during initial resuscitation consistently have shown poor outcomes.\textsuperscript{103–105}
### Pharmacologic agents for the treatment of secondary injury in acute SCI

#### Agents Directed at Free Radical Injury
- Vitamin E and selenium
  - Pretreatment of cats before SCI resulted in improved neurologic outcome and spinal cord blood flow following injury
- Tirilazad (21-aminosteroid)
  - Reduced spinal cord ischemia in cats
  - Effect not documented in dogs
- N-Acetylcysteine
  - No improvement in outcome in dogs with intervertebral disk herniation
- Sulfoxide and ε-aminocaproic acid
  - No improvement in outcome in dogs

Antioxidants require a prolonged period of administration to achieve therapeutic concentrations within the CNS, limiting their use in the acute phase of SCI

#### Agents Directed at Ionic Disturbances and Excitotoxicity
- Verapamil, diltiazem, nifedipine (calcium-channel antagonists)
  - Improved spinal cord blood flow in cats postinjury with diltiazem and nifedipine; not verapamil
- Sodium-channel blockers
  - Beneficial effects noted in experimental models
- NMDA and non-NMDA glutamate receptor antagonists
  - Delayed administration improved tissue sparing and functional recovery in rodent models
  - Most have adverse side effects and have largely failed clinical trials

#### Agents Directed at Inflammation
- Minocycline (second-generation tetracycline derivative)
  - Reduces activation of microglia and macrophages experimentally
  - Not yet evaluated in a trial
- Tacrolimus, cyclosporine, mycophenolate mofetil
  - Neuroprotective effects in experimental models of injury

#### Polyethylene Glycol
- Hydrophilic polymer that seals damaged neuronal membranes
- Evaluated in deep pain perception negative dogs; resulted in restored function in 60% of dogs
- Randomized, controlled trial in dogs currently underway

#### 4-Aminopyridine
- Potassium-channel blocker
  - Improves conduction by blocking the channels that would ordinarily be blocked by intact myelin
  - Improves conduction in vitro and vestibulospinal reflexes in cats
- Phase I clinical trial with 39 dogs with SCI
Supportive care

Supportive care of the patient with neurologic trauma should include the provision of dry, clean bedding; frequent turning; passive range of motion exercises; bladder care; ocular care (eg, frequent lubrication and inspection for corneal ulceration); and nutrition. Hypermetabolic states have been documented in patients with neurotrauma, and early feeding is recommended. The method of feeding should be based on the assessment of a patient’s ability to protect the airway. Although hyperglycemia has been associated with worsened mortality rates and neurologic outcome scores in humans with TBI and degree of hyperglycemia has been associated with severity of TBI in animals, intensive insulin therapy is not recommended for the control of hyperglycemia, based on the available human literature.

Bladder dysfunction is common in SCI patients, and depends on the location and severity of the lesion. Table 5 summarizes therapies for upper and lower motor neuron bladder dysfunction. Bladder care should include frequent (minimum every 12 hours) manual bladder expression or urinary catheterization. Compared with indwelling catheterization, intermittent urinary catheterization using a diligent aseptic technique is associated with a decreased risk of urinary tract infection, and there is no increased risk of infection with intermittent catheterization in comparison with manual expression.

Nonpharmacologic Strategies Specific for TBI

Decreasing cerebral blood volume

Elevation of the head by 15° to 30° reduces cerebral blood volume, thereby decreasing ICP and increasing CPP without harmful reductions in cerebral oxygenation. A stiff slant board should be used for head elevation to avoid bending of the neck and occlusion of the jugular veins. Elevation should not exceed 30°, as this can contribute to a decrease in CPP with associated effects on cerebral oxygenation.

<table>
<thead>
<tr>
<th>Table 5 Pharmacologic agents for bladder dysfunction</th>
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<tr>
<td><strong>Upper Motor Neuron Bladder</strong></td>
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<tr>
<td>α-Adrenergic antagonist</td>
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<td>Prazosin</td>
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<td>Phenoxybenzamine</td>
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<td>Skeletal muscle relaxant</td>
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<td>Diazepam</td>
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Therapeutic hypothermia

Many of the processes of neurotraumatic secondary injury are temperature dependent.116 TH, targeting temperatures of 32° to 34°C (89.6–93.2°F), decreases basal and cerebral metabolism, prevents apoptosis and necrosis and decreases cerebral edema formation and disruption of the BBB by decreasing release of excitotoxic amino acids (EAAs), decreases production of proinflammatory cytokines, and decreases excitatory signaling that can result in seizure activity.117 Therapeutic hypothermia is indicated as a second-line treatment in humans for intracranial hypertension and status epilepticus116,117; however, it has not gained widespread acceptance as a first-line treatment for TBI, likely because it is challenging to implement and has many potential complications.116,117 Few veterinary practices have the facilities to offer TH, but its successful use in a dog with protracted seizure activity associated with TBI has been described.78 As technologies for inducing TH and supporting patients being treated become more accessible in veterinary medicine, this therapy may gain more acceptance.

Decompressive craniectomy

Early craniotomy is indicated for evacuation of extra-axial hematomas. The role of decompressive craniectomy is more controversial in the management of TBI patients. It may be performed prophylactically at the time of mass evacuation if early craniotomy is performed, or later as a second-line, rescue therapy when medical management has failed.118 The results of the ongoing RESCUEicp trial may provide additional insight into the role of early decompressive craniectomy in the management of patients with TBI.119

Nonpharmacologic Strategies Specific for Acute SCI

Surgery is usually indicated in patients with moderate to severe deficits, neurologic deterioration, and/or instability of the vertebral column. Controversy exists regarding the best timing for surgical intervention in spinal cord trauma. Many traumatic SCI patients have extraspinal injuries that require initial stabilization. Nevertheless, earlier surgical treatment of human patients with traumatic SCI has been associated with improved outcomes.120–122

Management of vertebral fracture and luxation

The stability of spinal fractures in both humans and veterinary patients can be assessed using a 3-compartment model. This model divides the vertebral column into dorsal, middle, and ventral compartments, and a fracture is considered unstable when 2 or more compartments are disrupted. Table 6 lists the structures included in each of the 3 compartments.123,124

General indications for surgical management include moderate to severe neurologic deficits (eg, minimal to no motor function), evidence of vertebral column instability on imaging, and neurologic deterioration despite aggressive conservative management.13 Spinal cord decompression, reduction, and fixation are the aims of surgical management. There are many surgical techniques for stabilization of VFLs after reduction. The technique chosen depends on the location within the vertebral column, the type of fracture, and surgeon’s preference.123 Stabilization techniques include bone plates, screws, Steinmann pins, Kirschner wires, and polymethylmethacrylate (PMMA) cement.15 VFLs should be managed by board-certified orthopedic surgeons or neurosurgeons. Although surgical management is often indicated, return to function is generally shorter, and postoperative supportive care is generally less intensive than that required in conservative management, complications can occur, potentially leading to worsening of SCI. Worsening of SCI can occur with surgical manipulation,
loosening of implants, and implant failure or infection (particularly with PMMA). Revisi-
tional surgeries are, therefore, sometimes required.13

Conservative management of primary injury is most appropriate for patients with
minimal deficits, static disease, and good 3-compartment stability. External coapta-
tion has been described, but application of these devices is fraught with complications
including inadequate stabilization, increased mobility of VFL sites, and abrasions and
ulcerations. Conservative management, therefore, usually consists of strict cage rest
for 6 to 8 weeks, analgesia, and nursing care.

Traumatic intervertebral disk herniation
Patients who are nonambulatory, have progressive neurologic deficits, are nonrespon-
sive to conservative management, or have cervical lesions causing severe pain should
be considered for surgical management.34,125,126 With Type III (traumatic) interverte-
bral disk disease, surgical therapy is often not indicated unless there is an associated
compressive extra-axial hematoma. Depending on the site, degree of lateralization,
and severity of herniation, dorsal laminectomy, hemilaminectomy or ventral slot proce-
dures may be indicated.13,34,127–132

Conservative management can be used in treating patients with hyperpathia (neuro-
pathic pain) alone or with minimal neurologic deficits.13,34 It is recommended that strict
cage rest be instituted for a minimum of 4 to 6 weeks, although a recent retrospective
evaluation showed that the duration of rest in the management of thoracolumbar disk
disease had no effect on outcome or quality-of-life scores.133 Conservative manage-
ment is inappropriate for patients that are surgical candidates based on imaging and/
or have lost deep pain perception (DPP).34

Spinal cord contusion and extra-axial hemorrhage
A spinal cord contusion is an intraparenchymal hemorrhage that occurs most
commonly secondary to other causes of primary injury including VFLs, intervertebral
disk extrusion, and penetrating injuries.13,134 Therapy for parenchymal contusions is
aimed at treating concurrent primary injury (see earlier discussion).13 Extra-axial hem-
orrhage can occur epidurally or subdurally, and can cause direct compression to the
cord. It has also been reported secondary to intervertebral disk extrusion.135–137
Decompressive surgical techniques are recommended in patients with compressive
extra-axial hematomas.13

Cellular transplantation therapy
Intraspinal olfactory glial cell transplantation was evaluated in a phase I trial in 9 dogs
with thoracolumbar SCI caused by VFLs secondary to vehicular trauma or disk

<table>
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<th>Table 6</th>
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<tr>
<td>Three-compartment model for assessing stability of VFLs</td>
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<table>
<thead>
<tr>
<th>Dorsal Compartment</th>
<th>Middle Compartment</th>
<th>Ventral Compartment</th>
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<tbody>
<tr>
<td>Vertebral arch (spinous process, articular processes, laminae, pedicles)</td>
<td>Dorsal longitudinal ligament</td>
<td>Ventral portion of the vertebral body</td>
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<tr>
<td>Dorsal ligamentous complex (facet joint capsule, interarcuate ligaments, interspinous ligaments, supraspinous ligaments)</td>
<td>Dorsal aspect of the annulus fibrosus</td>
<td>Nucleus pulposus</td>
</tr>
<tr>
<td>Intertransverse ligaments</td>
<td>Dorsal cortex of the vertebral body</td>
<td>Ventral aspect of the annulus fibrosus Ventral longitudinal ligament</td>
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herniation (8 of 9 dogs were DPP negative). Significant functional improvement was noted in this small population of dogs, with 7 of 8 having improved motor function. A recent investigation of the safety of autologous bone marrow stromal cell transplantation in 7 dogs with severe acute SCI caused by VFL found this technique to be feasible and safe, with no complications noted. Two of 7 dogs were able to walk without support during follow-up (29–62 months after SCI). Although these techniques are currently in the early stages of development, they may represent new alternatives for patients with acute SCI.

Prognosis

Prognosis for recovery from neurotrauma depends on the severity of injury, the cause of injury, the site of the lesion, and the timing and efficacy of the treatment of primary and secondary injury. Small animals with neurologic trauma can demonstrate significant neurologic improvement and have a tremendous ability to compensate for neurologic deficits, so serial neurologic reassessments are recommended regardless of the presentation of the patient.

The MGCS can be used to assess prognosis for recovery in dogs with TBI, as it has been documented to be linearly associated with 48-hour survival. The presence of DPP has consistently been associated with improved outcome in acute SCI. A retrospective study evaluating severe thoracolumbar SCI in dogs showed that only 12% of dogs with VFL regained the ability to walk, whereas 69% of dogs with injury attributable to intervertebral disk herniation regained motor function. Surgical management of cases with thoracolumbar disk herniation and intact pain perception is excellent, with expected return of functional motor activity being 80% to 95% (reports range from 72% to 100%). In one study of surgically managed cervical disk herniation, the overall success rate was 99%. A retrospective study of dogs with cervical VFLs found that injuries that could be managed conservatively (ie, nonsurgically) had good functional outcomes in 90% of cases. Those requiring surgical management had a high risk of perioperative mortality (36%), but in those cases that survived the perioperative period the prognosis was excellent (100%). This same study also showed that nonambulatory patients and patients presented at more than 5 days after injury had worse prognoses. Prognostic studies in cats are limited, therefore much of the relevant information is extrapolated from dogs. Finally, neurotrauma rarely occurs independent of other systemic injury. It is therefore crucial to take the entire clinical picture of the patient into account when assessing prognosis and guiding owners in their decision-making process.

REFERENCES


