Hyperglycemia in dogs and cats with head trauma: 122 cases (1997–1999)

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Objective—To determine whether hyperglycemia is associated with head trauma in dogs and cats and whether the degree of hyperglycemia corresponds to severity of neurologic injury or outcome.

Design—Retrospective study.

Animals—52 dogs and 70 cats with head trauma and 122 age- and species-matched control dogs and cats.

Procedure—Severity of head trauma was classified as mild, moderate, or severe. Blood glucose concentrations recorded within 1 hour after admission were compared between case and control animals and among groups when case animals were grouped on the basis of severity of head trauma or outcome.

Results—Blood glucose concentration was significantly associated with severity of head trauma in dogs and cats and was significantly higher in dogs and cats with head trauma than in the control animals. However, blood glucose concentration was not associated with outcome.

Conclusions and Clinical Relevance—Results suggest that dogs and cats with head trauma may have hyperglycemia and that degree of hyperglycemia was associated with severity of head trauma. However, degree of hyperglycemia was not associated with outcome for dogs and cats with head trauma. Because hyperglycemia can potentiate neurologic injury, iatrogenic hyperglycemia should be avoided in patients with head trauma. (*J Am Vet Med Assoc* 2001;218:1124–1129)

In veterinary patients, brain injury can result from many types of trauma, including blunt vehicular trauma, bite wounds, falls from a height, crush injuries, and inadvertent or purposeful injuries from humans. Animals with traumatic brain injuries may have a variety of clinical signs, ranging from minor neurologic deficits to life-threatening neurologic impairment. Standardized neurologic scoring systems such as the Glasgow Coma Scale have been validated in human medicine and are used to quantitatively describe the severity of neurologic injury and aid in prognosticating outcome.[1-3] The Small Animal Coma Score was developed for veterinary patients to provide a standardized means to quantify the severity of neurologic injury and attempt to predict outcome.[4] This scoring system, however, has not been widely adopted in clinical veterinary practice. Instead, prediction of outcome for veterinary patients with traumatic brain injuries has largely been based on results of serial neurologic examinations and response to treatment in individual patients.

Primary brain injury refers to damage resulting directly from a traumatic insult. Following an injury, a cascade of biochemical reactions involving oxidative damage and inflammatory mediators may be initiated in the brain, perpetuating neurologic injury.[5-8] This process is referred to as secondary brain injury. Cerebral ischemia resulting from localized tissue disruption or systemic hypotension and hypoxemia has been shown to contribute substantially to development of secondary brain injury and to worsen outcome.[9-11] Ischemic brain damage is a frequent finding at autopsy in human patients with fatal traumatic brain injury[12,13] and is a common reason for secondary brain injury following trauma.[9,10]

Numerous reports suggest that hyperglycemia is associated with increased mortality rates or worsened neurologic outcomes in animals with experimentally induced head trauma[14,15] and human patients with head trauma.[16-25] Hyperglycemia has also been associated with increased mortality rates and worsened neurologic outcomes in dogs, cats, and other species with experimentally induced global or focal cerebral ischemia.[26-31] However, a cause-and-effect relationship between hyperglycemia and severity of neurologic injury or between hyperglycemia and outcome of patients with head trauma has not been established. It has been shown that hyperglycemia following head trauma results from a sympathoadrenal response to injury.[24,32-35] Therefore, the degree of hyperglycemia may simply reflect the severity of the injury sustained. Alternatively, experimental studies suggest that hyperglycemia actually potentiates neurologic injury. Although the exact mechanism by which hyperglycemia could perpetuate neurologic injury has not been clearly established, studies of animals and patients with cerebral ischemia have found that hyperglycemia increases free radical production,[36] excitatory amino acid release,[37] cerebral edema,[38] and cerebral acidosis[39] and alters the cerebral vasculature.[40]

An increase in cerebral acidosis is one of the most commonly cited mechanisms describing how hyperglycemia increases neurologic injury in patients with head trauma.[16-18,20,23-25] During ischemia, the brain initially relies on limited and inefficient anaerobic glycolysis in an attempt to maintain energy production, yielding only 2 moles of ATP and 2 moles of lactate ion/mole of glucose metabolized. Any ATP produced is rapidly consumed, leaving 2 moles of hydrogen ion as a by-product.[41] The accumulation of lactate and hydrogen ions causes extracellular and intracellular acidosis, which is cytotoxic to neurons and glial cells.[42-45] During periods of cerebral ischemia, hyperglycemia could

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potentially provide more substrate for anaerobic metabolism, resulting in an increase in cerebral acidosis and, subsequently, an increase in the severity of neurologic injury.[45,46]

The potential for hyperglycemia to cause harm has been suggested in recent reviews of the treatment of head trauma in veterinary patients.[47-50] However, to our knowledge, studies on the incidence or effect of hyperglycemia in veterinary patients with head trauma have not been published. The purpose of the study reported here, therefore, was to determine whether hyperglycemia is associated with head trauma in dogs and cats and whether degree of hyperglycemia corresponds with severity of neurologic injury or clinical outcome.

Criteria for Selection of Cases

Medical records of all cats and dogs examined by the Emergency Service of the Veterinary Hospital of the University of Pennsylvania between 1997 and 1999 in which a diagnosis of head trauma was made were reviewed. Cases were included in the study if the medical record was complete, if the dog or cat was examined by the Emergency Service within 12 hours after the traumatic incident and had not received any treatment to stabilize its condition prior to examination, and if blood glucose concentration was measured within 1 hour after admission. Cases were excluded if the dog or cat had previously been determined to have diabetes mellitus or had been receiving medication that could alter blood glucose concentration prior to admission (eg, glucocorticoids).[51,52]

Procedures

For each case animal included in the study, an age- and species-matched control animal was obtained by examining medical records of the veterinary hospital. Individual animals were considered for inclusion as control animals if the Emergency Service had examined them, blood glucose concentration had been measured within 1 hour after admission, there was no evidence of head trauma, and no treatment to stabilize the animal's condition had been instituted. Animals were excluded from consideration as control animals if they had a history of diabetes mellitus, had been receiving medication prior to admission that could alter blood glucose concentration (eg, glucocorticoids), or had evidence of hypoglycemia. Hypoglycemia was defined as a blood glucose concentration < 80 mg/dl with clinical signs consistent with hypoglycemia (eg, seizures, weakness) or a blood glucose concentration < 60 mg/dl in the absence of such clinical signs.

For each animal with head trauma included in the study, the following information was recorded: signalment, type of trauma, severity of head trauma, admission blood glucose concentration, and outcome. For age-matched control animals, the initial complaint and admission blood glucose concentration were recorded. Control animals were classified as having a traumatic or nontraumatic disorder.

The causes of head trauma were divided into 7 categories: blunt vehicular trauma, purposeful harm, penetrating wound, crush injury, fall from a height, unknown trauma, and other. Severity of head trauma was categorized as mild, moderate, or severe according to a modification of the Small Animal Coma Score. Patients were classified as having mild head trauma if they were ambulatory or paretic, had no changes in mentation or had signs of depression, had normal pupils or evidence of anisocoria with normal pupillary light responses, or had scleral hemorrhage, epistaxis, or abrasions and lacerations involving the head. Patients that had paresis or anisocoria secondary to an extracranial lesion (eg, a spinal cord or musculoskeletal disease) without other evidence for head trauma were excluded. Patients were classified as having moderate head trauma if they were recumbent, had a decreased level of consciousness but retained the ability to respond to noise or touch, or had anisocoria or miosis with slow pupillary light responses. Patients were classified as having severe head trauma if they were comatose or responsive only to noxious stimuli or had mydriatic pupils without a pupillary light response; they may also have had opisthotonus or seizures. If a patient had signs that spanned 2 categories of head trauma severity, the less severe score was assigned.

Outcome was recorded as alive, dead, euthanatized, or lost to follow up. Patients were classified as being alive if they had been discharged from the hospital with resolution or substantial improvement in neurologic signs or if telephone follow-up after discharge from the hospital was available. Patients were considered lost to follow-up if they were discharged from the hospital with substantial neurologic abnormalities and telephone follow-up was not possible.

Blood glucose concentration was determined, using anticoagulated whole blood, immediately after sample collection by use of the glucose oxidase enzymatic reaction[a] or a reagent strip and reflectance meter.[b] Most of the blood glucose concentration data were not normally distributed; therefore, nonparametric methods were used for statistical analyses, and results were reported as median and interquartile range (25th percentile to 75th percentile). Median admission blood glucose concentrations for patients with mild, moderate, and severe head trauma were compared by use of Kruskal-Wallis one-way ANOVA on ranks. This same method was used to compare admission blood glucose concentrations among groups when patients were grouped on the basis of outcome; dogs and cats lost to follow-up or euthanatized for reasons other than the underlying neurologic problem were not included in analyses of outcome. The Wilcoxon sign-rank test was used to compare admission blood glucose concentrations between case animals and all age-matched control animals, as well as between case animals and age-matched control animals examined because of a traumatic disorder. For all analyses, a value of $P \leq 0.05$ was considered significant.

Results

Two hundred ninety dogs and cats with head trauma were examined by the Emergency Service between 1997 and 1999; 122 (52 dogs and 70 cats) met the inclusion criteria. Most animals with head trauma excluded from the study were excluded because a

blood glucose concentration was not measured within 1 hour after admission, treatment to stabilize the animal's condition had been administered by the referring veterinarian, or neurologic function was inadequately defined.

There were 22 (42%) dogs of mixed breeding, 6 (12%) American Pit Bull Terriers, 5 (10%) Toy Poodles, 4 (8%) Chihuahuas, 2 (4%) German Shepherd Dogs, 2 (4%) Yorkshire Terriers, and 1 each of the following breeds: Beagle, Bouvier des Flandres, Chow Chow, Cocker Spaniel, Giant Schnauzer, Lhasa Apso, Miniature Poodle, Rhodesian Ridgeback, Smooth Fox Terrier, and Wire Fox Terrier. All cats included were domestic shorthair cats. Median age of the dogs with head trauma was 2 years (interquartile range, 0.5 to 6 years); median age of the cats with head trauma was 0.21 years (0.13 to 0.5 years). Age was not recorded for 3 dogs and 1 cat. Twenty-seven (52%) dogs were female (5 spayed) and 24 (46%) were male (6 castrated). Forty (57%) cats were female (4 spayed) and 28 (40%) were male (6 castrated). Sex of 1 dog and 2 cats was not recorded. Most dogs were examined because of blunt vehicular trauma; most cats were examined because of a crush injury (**Table 1**).

Thirty-three of the 52 (63%) control dogs and 27 of the 70 (39%) control cats were examined because of other trauma. Initial complaints for the 19 control dogs with nontraumatic disorders included gastrointestinal tract disease (n = 3), neurologic disease (2), infection (4), ophthalmologic disease (1), hematologic disease (2), neoplasia (1), and other (6). Initial complaints for the 43 control cats with nontraumatic disorders included gastrointestinal tract disease (n = 18), neurologic disease (3), ophthalmologic disease (2), hematologic disease (2), respiratory tract disease (4), cardiovascular disease (1), infection (3), and other (10).

There were 20 (38%) dogs with mild, 20 (38%) dogs with moderate, and 12 (23%) dogs with severe head trauma. Twenty-five (36%) cats had mild, 21 (30%) cats had moderate, and 24 (34%) cats had severe head trauma.

Median admission blood glucose concentrations for dogs with mild, moderate, and severe head trauma were 145, 160, and 242 mg/dl, respectively (**Fig 1**). Median admission blood glucose concentrations for age- and species-matched control dogs for the dogs with mild, moderate, and severe head trauma were 115, 118, and 126 mg/dl, respectively.

Median admission blood glucose concentrations for cats with mild, moderate, and severe head trauma were 150, 222, and 219 mg/dl, respectively (**Fig 2**). Median admission blood glucose concentrations for age- and species-matched control cats for the cats with mild, moderate, and severe head trauma were 122, 127, and 131 mg/dl, respectively.

Admission blood glucose concentration was significantly associated with severity of head trauma in both dogs ($P = 0.012$) and cats ($P = 0.015$). Admission blood glucose concentration for cats with mild head trauma was significantly different from concentration

Table 1—Major causes of head trauma in 52 dogs and 70 cats examined at a veterinary teaching hospital

Cause of head injury	No. of dogs	No. of cats
Blunt vehicular trauma	27	6
Purposeful harm	9	6
Crush injury	6	33
Penetrating wounds	3	6
Fall from a height	2	5
Unknown	3	12
Other	2	2

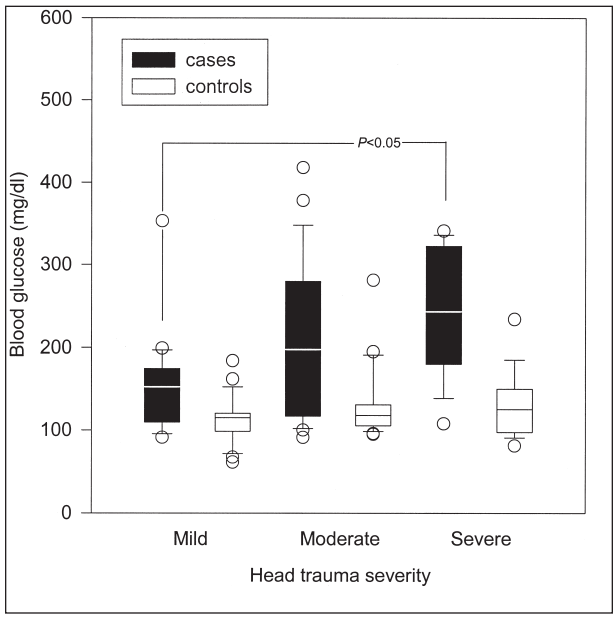

Figure 1—Box-and-whisker plots of blood glucose concentrations at the time of admission in 52 dogs with head trauma, grouped on the basis of severity of injury (cases), and of 52 age-matched control dogs (controls). The horizontal line in each box represents the median value. The boxes themselves represent the 25th to 75th percentile (ie, the middle 50% of the data). The whiskers represent the 10th to 90th percentile (ie, the middle 80% of the data). Circles represent outliers.

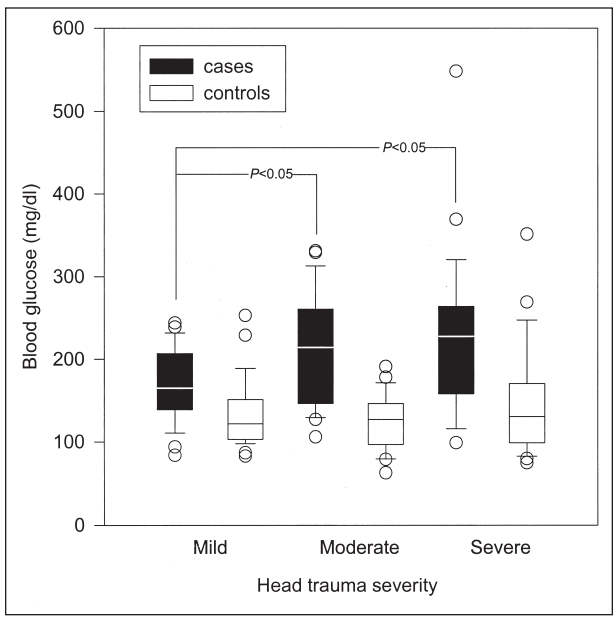

Figure 2—Box-and-whisker plots of blood glucose concentrations at the time of admission in 70 cats with head trauma (cases) and of 70 age-matched control cats (controls). *See* Figure 1 for key.

for cats with moderate head trauma and from concentration for cats with severe head trauma. For the dogs, a significant difference in admission blood glucose concentration was detected only between those with mild and severe head trauma.

Median admission blood glucose concentrations for dogs and cats with head trauma were significantly ($P < 0.001$) higher than median admission blood glucose concentrations for the age-matched control dogs and cats.

The subgroup of case dogs for which age-matched control dogs were examined because of a traumatic disorder included 10 dogs with mild, 13 dogs with moderate, and 10 dogs with severe head trauma. Median admission blood glucose concentrations were 149 mg/dl (interquartile range, 109 to 171 mg/dl), 139 mg/dl (104 to 207 mg/dl), and 242 mg/dl (196 to 321 mg/dl) for dogs with mild, moderate, and severe head trauma, respectively. Median admission blood glucose concentrations for the corresponding control dogs were 119 mg/dl (99 to 119 mg/dl), 122 mg/dl (111 to 161 mg/dl), and 126 mg/dl (96 to 156 mg/dl), respectively. Admission blood glucose concentration for dogs with severe head trauma was significantly ($P = 0.014$) different from concentration for age-matched control dogs. However, admission blood glucose concentrations for dogs with mild or moderate head trauma were not significantly different from values for the control dogs.

The subgroup of case cats for which age-matched control cats were examined because of a traumatic disorder included 10 cats with mild, 9 cats with moderate, and 8 cats with severe head trauma. Median admission blood glucose concentrations were 167 mg/dl (141 to 206 mg/dl), 190 mg/dl (141 to 302 mg/dl), and 240 mg/dl (175.5 to 342 mg/dl) for cats with mild, moderate, and severe head trauma, respectively. Median admission blood glucose concentrations for the corresponding control cats were 115 mg/dl (103 to 151 mg/dl), 137 mg/dl (112 to 157 mg/dl), and 156 mg/dl (115 to 191 mg/dl), respectively. Admission blood glucose concentration for cats with moderate head trauma was significantly ($P = 0.05$) different from concentration for age-matched control cats. Admission blood glucose concentrations for cats with mild or severe head trauma were not significantly different from values for control cats. However, the power of these analyses was limited by the small number of cases.

Of the 20 dogs with mild head trauma, 18 (90%) lived, 1 (5%) was euthanatized, and 1 (5%) was lost to follow-up. Of the 20 dogs with moderate head trauma, 15 (75%) lived, 1 (5%) died, 3 (15%) were euthanatized, and 1 (5%) was lost to follow-up. Of the 12 dogs with severe head trauma, 3 (25%) lived, 1 (8%) died, and 8 (67%) were euthanatized. One dog with mild head trauma and 1 dog with moderate head trauma were euthanatized for reasons other than severity of neurologic injury.

Of the 25 cats with mild head trauma, 23 (92%) lived and 2 (8%) were lost to follow-up. Of the 21 cats with moderate head trauma, 9 (43%) lived, 1 (5%) died, and 11 (52%) were lost to follow-up. Of the 24 cats with severe head trauma, 2 (8%) lived, 8 (33%) died, 9 (38%) were euthanatized, and 5 (21%) were lost to follow up.

For analyses of outcome, only the 36 dogs that lived, 2 that died, and 10 that were euthanatized were included. Two dogs that were lost to follow-up and 2 that were euthanatized for reasons other than severity of neurologic injury were excluded. For dogs that lived, median admission blood glucose concentration was 151 mg/dl (123 to 203 mg/dl). For dogs that died, median admission blood glucose concentration was 271 mg/dl (164 to 378 mg/dl). For dogs that were euthanatized, median admission blood glucose concentration was 205 mg/dl (117 to 321 mg/dl). Median admission blood glucose concentrations were not significantly different among groups when dogs were grouped on the basis of outcome.

Similar results were obtained when admission blood glucose concentrations were compared with outcome of cats. Thirty-four cats that lived, 9 that died, and 9 that were euthanatized were included in this analysis. The 18 cats that were lost to follow-up were excluded from this analysis. Median admission blood glucose concentration for cats that lived was 192 mg/dl (140 to 242 mg/dl), compared with 209 mg/dl (173 to 256 mg/dl) for cats that died and 212 mg/dl (141 to 256 mg/dl) for cats that were euthanatized. Median admission blood glucose concentrations were not significantly different among these 3 groups.

Discussion

Results of the present study indicate that dogs and cats with head trauma may have hyperglycemia and that degree of hyperglycemia is associated with severity of head trauma. However, degree of hyperglycemia was not associated with outcome of the dogs and cats with head trauma in this study.

Development of hyperglycemia following head trauma in dogs and cats is consistent with results of clinical studies involving human patients with head trauma[16-25] and experimental studies involving animals.[14,15] The hyperglycemic response following head trauma is considered a stress response to injury resulting in many metabolic alterations. Experimental studies of head injury in cats[32,33] and clinical studies of head trauma in humans[24,34,35] have shown that serum concentration or urinary excretion of catecholamines, glucagon, and cortisol is markedly elevated following head trauma and remains elevated for several days after injury. It has been postulated that this sympathoadrenal response following head trauma is responsible for the hyperglycemia seen clinically.

The high blood glucose concentrations in dogs and cats with head trauma in the present study were likely not simply a generalized stress response to hospitalization, because median admission blood glucose concentration for the control animals was significantly lower than that for the animals with head trauma. Control animals were matched with case animals on the basis of age to reduce the influence of age on any stress response.

In the present study, we were not able to completely control for the effect of the stress response to trauma on degree of hyperglycemia. Subgroup analysis of case animals with age-matched control animals examined because of a traumatic disorder revealed sig-

nificant differences in blood glucose concentrations between cats with moderate head trauma and control cats and between dogs with severe head trauma and control dogs. This suggests that hyperglycemia in patients with head trauma may develop independently from the stress response to generalized trauma. Our inability to detect other significant differences during subgroup analyses (eg, between cats with mild or severe head trauma and control cats and between dogs with mild or moderate head trauma and control dogs) may simply have been a result of the small number of cases included; the power for this analysis was < 0.8.

Dogs with severe head trauma and cats with moderate or severe head trauma had significantly higher admission blood glucose concentrations than did those with mild head trauma. These results are consistent with findings of human clinical studies in which a higher admission blood glucose concentration was associated with a lower Glasgow Coma Score (ie, more severe injury) on admission.[15,17,18,20,23-25] A study of head trauma in children concluded that hyperglycemia was not associated with severity of neurologic injury[53]; however, this study defined hyperglycemia as a blood glucose concentration > 270 mg/dl. This high threshold for hyperglycemia may have underestimated the true incidence of hyperglycemia in this population and introduced a bias in comparing incidence of hyperglycemia to severity of neurologic injury. Whether hyperglycemia is a cause or result of more severe neurologic injury could not be determined in the present study because of its retrospective nature.

We did not identify an association between admission blood glucose concentration and outcome in the present study, possibly because of the number of cases lost to follow up that were not included in the outcome analysis. Additionally, because few animals died, the population size may have been too small to identify a significant association. Our findings are in contrast to the results of many retrospective studies of human patients, which report that admission blood glucose concentrations correlate with outcome in patients with head injuries.[16,20-25] Other studies have found persistence of hyperglycemia beyond 24 hours after injury to be strongly associated with a higher mortality rate or poorer outcome.[16,17,19] Serial blood glucose concentrations were not consistently available in the present study, making evaluation of these data impossible. Nevertheless, duration of hyperglycemia may be an important consideration in determining outcome of veterinary patients.

There are a number of limitations to the present study. Severity of head trauma was graded on the basis of interpretations of entries made in the medical records by various clinicians. Inaccuracies in recording of neurologic abnormalities in the original medical record or misinterpretations of the medical records may have resulted in inappropriate classification of severity. A number of animals were discharged from the hospital with persistent neurologic dysfunction but were lost to follow up and, therefore, excluded from outcome analysis. In addition, because not all control animals were examined because of traumatic disorders and because there was not a means of comparing severity of trauma between control animals and animals with head trauma, we cannot rule out the possibility that hyperglycemia was simply a general response to severe trauma.

Although hyperglycemia could not be associated with outcome in the present study, it is important to remain cognizant of the possibility that hyperglycemia may potentiate neurologic injury, particularly in patients at risk for secondary neurologic injury. Control of blood glucose concentrations with insulin was not investigated in this study and is not being recommended. However, given that hyperglycemia has been shown to have deleterious effects in patients with head injury, efforts should be made to prevent iatrogenic hyperglycemia in these patients. Thus, administration of dextrose solutions and medications that could exacerbate hyperglycemia, such as corticosteroids, should be avoided or minimized. Future investigations evaluating neurologic scores prospectively and serial blood glucose concentrations in patients with isolated head trauma are necessary to more clearly characterize the association between hyperglycemia and outcome in these patients.

[a]Stat Profile, NOVA Biomedical, Waltham, Mass.
[b]Glucometer III, Miles Inc, Elkhart, Ind.

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