A traumatic head injury study in raptors of rehabilitation treatment protocols. Should we be taking a second look at steroids?

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ABSTRACT:
History provided us the ability to monitor the evolution of treatment protocols over time. We reviewed raptor traumatic brain injury (TBI) protocols, specifically the use of steroids. The trends are to derive avian treatment protocols from the interpretation of human clinical trials. The interpretations shift treatment protocols radically rather than conservatively, based on quantified outcome data. Each trial utilized a dramatically different steroid dose, frequency, and duration. Through an outcomes survey of wildlife rehabilitators worldwide, we are taking a second look at steroids.

Keywords: raptor, traumatic brain injury (TBI), steroid, rehabilitation, head injury, dexamethasone, methylprednisolone, prednisolone, avian

The use of corticosteroids in cases of traumatic brain injury (TBI) has been a controversial subject in both human and animal medicine. Many emergency room clinicians, as well as wildlife rehabilitators have used common steroid drugs such as dexamethasone, decadron, methylprednisolone, and prednisolone. In the past decade, the use of these and other corticosteroids has been questioned. Some of the re-evaluations of corticosteroid treatments have resulted in the call to end steroid use in TBI patients, both animals and human, altogether (Pokras and Murray 2008, Roberts et al. 2004). Human outcomes may not necessarily relate to avian medicine in that avian TBI patients often present with significant pre-existing conditions, which result in increased morbidity, secondary to steroid administration. After reviewing all the published clinical trials, our question remains: Within the realm of wildlife rehabilitation is there ever a time that any steroids are appropriate in the treatment of traumatic head injury? If so what type, dose, and frequency?

Since the 1960s, steroid treatment protocols have been an option for emergency room doctors with TBI patients. In clinical models, steroids were utilized for reinstating normal vascular permeability, decreasing cerebrospinal fluid production, and reducing free radical production (Bullock and Polvishock 2007). Glucocorticoids in particular were standard treatment protocol for brain edema and TBI, as well as in the management of brain tumors (French and Galicich 1964). In the 1970s, high-dose steroids became common use for human TBI cases. Several studies arose in the 1980s concerning the use of corticosteroids for severe brain trauma that disputed the effectiveness of such medications. These studies concluded that administration of high-dose steroids to TBI patients did not result in any significant change in prognosis, nor did there appear to be any benefits to their use (Braakman et al. 1983, Cooper et al. 1979, Dearden et al. 1986, Giannotta et al. 1984, Gudeman et al. 1979, Saul et al. 1981). The CRASH (Corticosteroid Randomization After Significant Head Injury) study revealed that high-dose methylprednisolone in TBI patients resulted in a slightly increased mortality rate (21%) versus that of the control group (18%) (Roberts et al. 2004). These results relate to

raptor rehabilitation in that avian medical protocols tend to follow human medical guidelines. However, the interpretations of scientific studies made by both veterinarians and wildlife rehabilitators vary widely. Many wildlife rehabilitators follow the interpretation of the CRASH study and have stopped using all steroids. Others feel that detailed neurological exams should be the basis for determining whether or not to use steroids. Still other rehabilitators feel that since dexamethasone is a long lasting drug, that the only steroid that might be appropriately used is the short acting methylprednisolone (Marla Lichtenberger, DVM, Dipl. ACVECC and Lori Arent, MS).

A major concern of using corticosteroids in raptors is the immunosuppressive effect of these drugs. Corticosteroids repress T and B lymphocytes in the spleen, thymus, and bursa of Fabricius. This alteration in both cell-mediated and humoral immunity may predispose the patient to secondary bacterial, viral, parasitic and/or fungal infections (Hess 2002). Raptors in particular are already prone to decreased immune system response and are often found with preexisting conditions that resulted in their subsequent head trauma. Corticosteroid treatments can potentially interfere with secondary wound and fracture repair due to the inhibition of the chemotaxis of inflammatory mediator cells, such as macrophages and neutrophils (Hess 2002).

According to Dr. Mary Ann Cooper, MD, Professor, Department of Emergency Medicine, University of Illinois, Chicago, *"Steroids are still given before the trauma (surgery) or for swelling around brain tumors and similar problems - neither of which work for after head trauma."* TBI treatment of human patients on arrival to the emergency room is guided by nuclear medicine findings. Unfortunately, we do not have these same options to determine the best course of treatment in avian medicine. Cutting edge treatment of TBI in humans leads towards neuroprotective steroids, such as progesterone. The recent ProTECT (Progesterone for Traumatic brain injury--Experimental Clinical Treatment) trial used randomization of TBI human patients to either a placebo or progesterone therapy following traumatic head injury (Wright et al. 2006). They based their trial on animal studies that found that progesterone could be beneficial for reducing cerebral edema, moderating inflammatory mediator cells and cytokine release, lowering neuronal apoptosis, and increased recovery from severe neurological trauma (Wright et al. 2006). The ProTECT study data showed that TBI patients treated with progesterone had a lower 30-day mortality rate than those treated with placebo. The use of progesterone also gave patients with acute TBI a better chance of a favorable neurological outcome (Wright et al. 2006).

Dr. Donald Stein, PhD, Professor of Emergency Medicine and neurobiologist at Emory University, discovered the neuroprotective properties of progesterone. He and members of his lab have been studying progesterone for almost twenty years in laboratory rats; however, a trial using avian species would be beneficial, since TBI and concussion occur in an extremely high frequency (80%) of raptors admitted to wildlife facilities (Casey and Casey 2000). According to Dr. Stein the pre-ectropic actions of medroxyprogesterone acetate (MPA) manufactured under the trade names Provera, Cycrin, Depo Provera, decrease shock through action on multiple receptor sites. A dose of 8-16 mg per kg IM on

arrival followed by a daily injection given SQ on a tapered dosage scale was used in laboratory rats. A similar dosage may be applicable to raptors.

In a telephone interview with Dr. Stein, he shared an anecdote about a Bichon Frise dog. The dog was critically hydrocephalic and the veterinarian, after exhausting all treatment options, was recommending euthanasia. Dr. Stein contacted the veterinarian personally to discuss his current research and recommended that the veterinarian try progesterone versus euthanasia. The dog was given a three-day course and after the third day had completely recovered. The dog is currently maintained with a single dose of progesterone every six months (Stein 2008). Dr. Stein continues his research into the use of progesterone, which has tremendous potential for the treatment of TBI in veterinary patients, including wildlife.

RESULTS:

Our data reveals a majority of the contributing facilities have used steroids in some form or other. About 60% of the TBI protocols reported involved steroid use. Protocols range from a single injection of dexamethasone upon arrival, to continued steroid therapy (IM, SQ, or PO) over the course of a few days or weeks. Each of these categories had an almost 50% survival rate (includes both released and non-released birds) of raptors treated. Interpreting this data may result in false positives due to the large number of steroid protocols in which dosage and duration were unknown (70%) (figure 2). The highest percentage of reported steroid treatment was an initial dose of dexamethasone tapered over 2-5 days. Many facilities evaluate individual TBI on arrival and adjust their protocol based on the extent and severity of the injury. This exam determines whether the raptor receives only one dose of a steroid, a week of treatment, or no steroid at all. At Washington State University Veterinary Teaching Hospital Dr Nicky P Finch uses steroids for TBI "*Usually once a day (I use dexamethasone since it's cheap, can't afford some of the others), and usually for not more than 3 days. If they seem totally recovered after one dose, we won't usually give another. If they haven't improved at all after 2 doses, I usually wont give a 3rd either. Raptors are not as sensitive to the immunosuppressive effects as psittacines are, but I still try to limit the length that I treat them. We give between 2 - 6mg/kg (usually around the 4 - 5mg/kg mark) and will do so IV or IM.*"

Overall, looking at steroid protocols as a single category 106 of the 218 raptors treated with steroids survived (figure 1), which can be interpreted as 48.6% success rate. Those facilities that used steroids as a treatment of last resort resulted in the highest death rates.

More data was submitted for the non-steroid treated group. The most successful protocol is the use of non-steroidal medications, resulting >50% survival rate. Homeopathic remedies have been 100% successful in the two cases submitted. It is possible that birds contained within the unknown protocol category without steroids were also treated with homeopathic remedies but that cannot be determined based on our data. Raptors treated without medication and only with heat had a survival rate of >40%. Some rehabilitators feel that heat is not an appropriate treatment for TBI and that hypothermia, by ice and cold packs, is actually better for improvement of the injury (Pokras and Murray 2008).

For non-steroid protocols as a whole, 41.9% of raptors treated survived. This is 7% less than the survival rate of raptors treated with steroids.

CONCLUSION:

Though this data cannot prove significant benefit of any treatment protocol it does confirm that the whole subject is worth a second look. Most facilities that contributed to this study did not only fall within one protocol category, but instead used varied protocols based on individual evaluation. Future studies could differentiate between protocols and clarify outcome trends. There may never be one correct protocol to treat TBI. It may prove that varying degrees of steroid use and/or neuroprotective steroids are appropriate. Progesterone therapy shows great promise for TBI and should be evaluated for avian use.

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Figure 1:

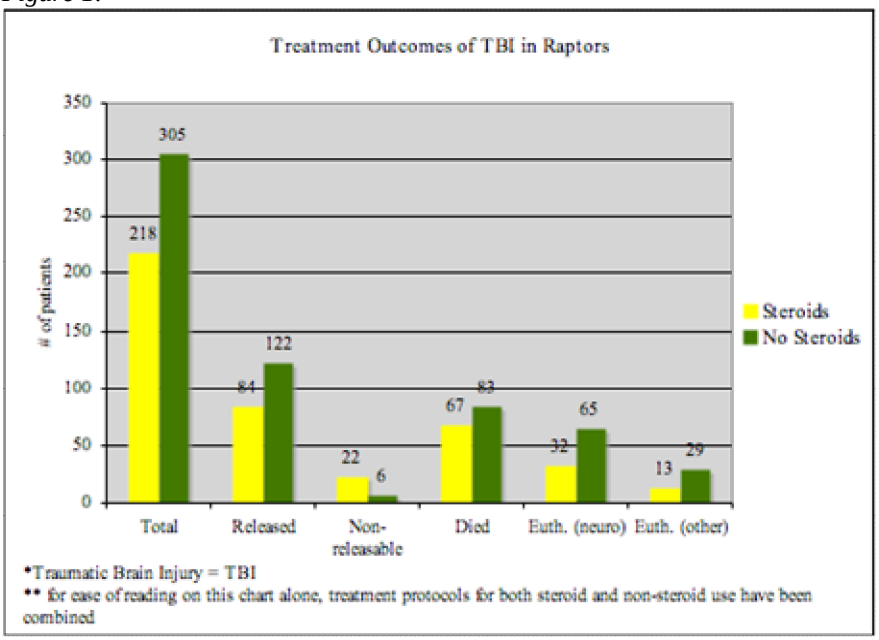
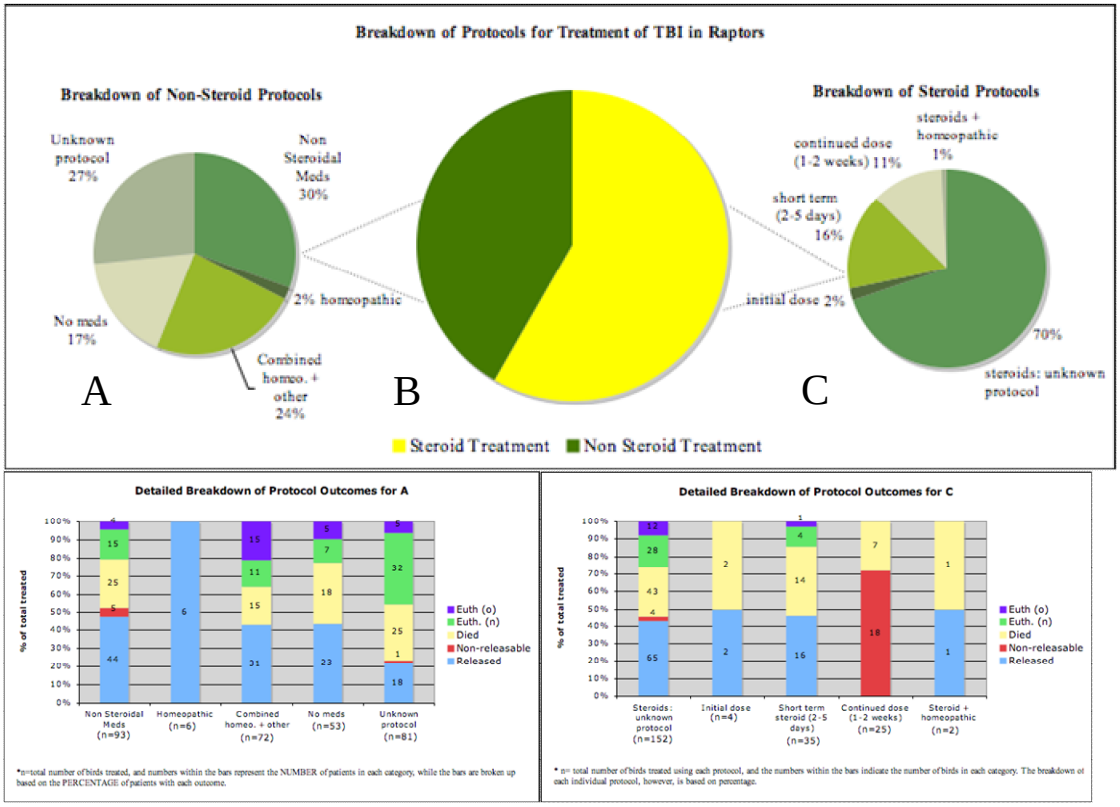


Figure 1. Relative breakdown of our two general categories, treatment protocols with and without steroids, based on outcome.

Figure 2:



(above) The varied protocols used to treat TBI in raptors are broken down first by whether or not they involved steroids, then further by protocol. See appendix for details of each protocol. The two bar graphs further breakdown charts A (left) and B(right) to specific outcomes of raptors treated with each protocol by both number and percentage.

APPENDIX I:

Detailed protocol info:

No steroids:

- Non steroidal meds: protocols under this category include the administration of analgesics and NSAIDs mainly, including metacam, banamine, butorphanol, buprenorphine, and traumeel. Both oral and injectible medications were used. Success: of 93, 53% survived. Used by: Wild at Heart Wildlife Rehabilitation, Raptor Center of University of Minnesota, Wolf Hollow, Wildcare, Three Ring Ranch
- Homeopathic: these include both arnica and hypericum. Success: of 6, 100% survived. Used by: Wolf Hollow
- Combined homeopathic and non-steroidal meds: protocols under this category include a combination of the above listed homeopathic and non-steroidal treatments. Success: of 72, 43% survived. Used by: Wolf Hollow, TriState bird rescue and research inc.
- No meds: these protocols consist of free choice heat and no additional medications or treatments. Success: of 53, 43% survived. Used by: Wolf Hollow, Prince Rupert Wildlife Rehabilitation, Wildcare, Alaska Raptor Center.
- Unknown protocol: these are known to use non-steroidal medications and treatments, but the exact protocols are unknown. Success: of 81, 23.4% survived. Used by: Audubon center for Birds of Prey, Alaska raptor center

Steroids:

- Initial dose of steroids: protocols in this category involved a single, initial dose of dexamethasone upon arrival, given SQ. No other steroids were given. Success: of 4, 50% survived. Used by: Wolf Hollow, 3RR
- Short term steroid use (2-5 days): these protocols involved an initial, higher dose of Dex (generally 4mg/kg) followed by either a second half-dose 12 hours later, or tapering doses over the course of a few days. Doses were generally found to be between 2-4 mg/kg depending on the size of the raptor. Success: of 35, 46% survived. Used by: Kaeser, 3RR, Wolf Hollow, Washington State University, Animal Rehabilitators Alliance
- Continued steroid use (1-2 weeks): this protocol involved a 2-4 mg/kg dose of dex IM SID for up to a week. Success: of 25, 72% survived. Used by: Veterinary and Medicine Teaching Hospital at Artistotle University (Greece)
- Steroids + homeopathic: this involves a single dex dose combined with homeopathic remedies. Success: of 2, 50% survived. Used by: Wolf Hollow
- Unknown steroid protocol: the protocols in this category are known to use a steroid (known ones are dex, prednisone, decadron, and solu delta cortef), but duration and dosage are unknown. Success: of 152, 45% survived. Used by: Tri State Bird Rescue and Research inc., Nature Discovery Center, Wildcare, Alaska Raptor Center, SB Wildlife Rehabilitation.

APPENDIX II:

Timeline of the use of steroids in TBI based on human clinical trials

1960: Woodford, a veterinarian, states, “no one has the slightest idea of the cause of these convulsions or how to treat them” in regards to neurological trauma symptoms in raptors

1960s: steroids are introduced as a treatment for brain edema in humans

1960s: based on experimental evidence by French and Galicich showing glucocorticoids had many beneficial effects, especially in brain tumor patients, glucocorticoids become commonly administered. They are used in patients undergoing a variety of neurosurgical procedures and are also common treatment for severe TBI.

1976: 2 studies performed on the effects of steroids and severe TBI:

- Gobiet et al. does a study with low and high dose Decadron compared to a control group of severe TBI and finds high doses to be beneficial
- Faupel et al. does a double-blind study with glucocorticoids and finds a favorable dose-related affect on mortality.

1979: Cooper et al. perform a double-blind study using dexamethasone in humans with severe TBI. A placebo as well as low and high dose dex is used. They are able to measure ICP in 51 of the 97 patients and find no significant difference in outcome or ICP.

1981: Saul et al. perform a clinical trial of methylprednisolone involving 100 patients. They find no significant difference in outcome over a 6-month period, but the steroid-treated group shows better outcomes within a subgroup of patients who improved over the first 3 days.

1984: Gianotta et al. perform another double-blind study of methylprednisolone using a placebo as well as high and low tapering doses. They again find no significant benefit, but when comparing steroid levels find that high dose groups showed increased survival and improved speech function over low dose groups.

1986: references in textbooks, including “Clinical Avian Medicine and Surgery” by Harrison and Harrison, recommend steroids to treat TBI in birds which may be beneficial following an initial application of ice or cold packs to the head.

1994: Gaab et al. perform a double-blind study involving 300 patients using a placebo and high dose tapering dexamethasone initiating within 3 hours of injury. Their study shows no significant benefit to the steroid.

1997: Anderson et al. analyze the results of past studies on corticosteroids in TBI and find no significant affect of steroids on improving the outcome of TBI. They suggest a larger study be done.

1998: Marshall et al. perform a large randomized study using a synthetic steroid (tirilazad mesylate). They use 1,170 patients but again find no overall benefit to the steroid over the placebo.

2002: “Birds of Prey” by John E. Cooper recommends corticosteroids in the treatment of neurological disorders in raptors caused by infectious diseases. They are also recommended to alleviate certain clinical signs of central nervous system trauma but not as the main protocol, only in addition to other supportive forms of treatment

2004: Watson et al. do a follow up study on first late seizures in patients who have been treated with steroids for TBI. They find a 74% increased risk of developing these seizures in patients who have been treated with glucocorticoids within 24 hrs of injury as opposed to those treated 2-7 days after. However, they find no significant difference in mortality among patients.

2004- CRASH study (Corticosteroid Randomization after Significant Head Injury) is an international randomization study using 10, 008 patients from 239 hospitals. It looks at the effects of methylprednisolone by administering an initial dose (2mg IV) and a follow-up dose of 0.4 mg/h for 48 hours. All patients were admitted within 8 hours of their injury. The study halts after 5 years and 2 months after methylprednisolone is found to be damaging and not beneficial. However, they are unclear about the cause of death in the majority of patients, and are unsure if it is related to the use of methylprednisolone or

other factors. This study becomes an important steroid study and is the basis of many steroid protocols in affect after this time, including those in the veterinary field.

2006: Progesterone is found to be beneficial for TBI in humans. The study finds patients treated with progesterone have a lower 30-day mortality rate and a more favorable neurological outcome. Progesterone has been studied in animals for over 15 years, but this 3-year study is the first trial in humans.

2008: "Throw away your dex" by Mark A. Pokras, DVM and Maureen Murray, DVM from Tufts University, calls for the cessation of the use of dexamethasone to treat head trauma in raptors due to its deleterious effects, including increased risks of GI bleeding, infection, an increase in blood glucose, and immunosuppression. This recommendation is based on the human CRASH study. The article notes that methyprednisolone, which is rapidly metabolized, has been proven beneficial in the treatment of spinal cord trauma when used 0-4 hours after injury. They suggest support via fluids and NO heat, but do note that it requires further study to know for sure and that each head injury is different.

2008: facilities worldwide are using varied protocols to treat TBI in raptors, and many have taken up the trend of moving away from steroids. Though some still incorporate steroid use into their treatment protocols, many only use it as a "hail Mary" with their worst cases.

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