WORKSHEET for Evidence-Based Review of Science for Veterinary CPCR

1. Basic Demographics

Worksheet author(s)

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[redacted]

2. Clinical question:

In dogs and cats during cardiac arrest (P), does treatment with corticosteroids alone or in combination with other drugs (I) as opposed to care without corticosteroids (C), improve outcome (O) (e.g., survival or neurological status)?

3. Conflict of interest specific to this question:

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet?

None

4. Search strategy (including electronic databases searched):

4a. Databases

MEDLINE via PubMed (1950 to March 2011)

1. heart arrest
2. cardiac arrest
3. cardiopulmonary resuscitation or CPR or CPCR
4. (steroid or corticosteroid or hydrocortisone or prednisone or prednisolone or methylprednisolone or dexamethasone) or (steroids or corticosteroids or hydrocortisone or prednisone or prednisolone or methylprednisolone or dexamethasone)
9. 1 or 2 or 3

10. 4 and 9: 987 citations
11. Limit 10 to (human OR animal) AND (clinical trial): 7 relevant citations

4b. Other sources

None

4c. State inclusion and exclusion criteria for choosing studies and list number of studies excluded per criterion

Inclusion criteria

All human and animal studies evaluating the use of corticosteroids during the ALS phase of cardiac arrest resuscitation where a clinical outcome (ROSC or mortality or neurological function or survival) is one of the study endpoints.

Exclusion criteria

Abstracts only. Editorials. Therapy with corticosteroids administered before arrest or during post-arrest care.

4d. Number of articles/sources meeting criteria for further review: 7

-2 relevant animal studies were identified: (Smithline 1993 [prospective randomized placebo-controlled rodent experimental study] and Hofmeister 2009 [retrospective review of clinical cases]).

-2 randomized human trials were identified: (Mentzelopoulos 2009 [prospective double-blinded placebo-controlled] and Paris 1984 [prospective blinded placebo-controlled]).

-3 relevant human studies were identified: (Tsai 2007 [prospective nonrandomized open-label trial], White 1976 [small case series], and White 1979 [retrospective review of clinical cases]).

5. Summary of evidence

Evidence Supporting Clinical Question

Good						
Fair			Smithline (A)	Hofmeister (A, B, C, D)		*White 1979(A)*
Poor						*Mentzelopoulos (A, C, E); Tsai (A)*
	1	**2**	**3**	**4**	**5**	**6**
Level of evidence (P)						

A = Return of spontaneous circulation C = Survival to hospital discharge E = Other endpoint
B = Survival of event D = Intact neurological survival *Italics = Non-target species studies*

Evidence Neutral to Clinical question

Good						
Fair						
Poor						*White 1976 (A)*
	1	**2**	**3**	**4**	**5**	**6**
Level of evidence (P)						

A = Return of spontaneous circulation C = Survival to hospital discharge E = Other endpoint
B = Survival of event D = Intact neurological survival *Italics = Non-target species studies*

Evidence Opposing Clinical Question

Good						
Fair						*Paris (A)*
Poor						
	1	**2**	**3**	**4**	**5**	**6**
Level of evidence (P)						

A = Return of spontaneous circulation C = Survival to hospital discharge E = Other endpoint
B = Survival of event D = Intact neurological survival *Italics = Non-target species studies*

6. REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

Data to support the use of corticosteroids in veterinary patients during the Advanced Life Support phase of CPCR is equivocal, with a very limited amount of data suggesting a beneficial effect of steroid use. However, data appear promising, and further carefully controlled clinical trials are necessary before widespread use of corticosteroids can be recommended, despite the challenges inherent in designing a study in clinical patients during CPA.

There are no data that clearly demonstrate a negative effect of corticosteroid use in veterinary or human patients when used during ALS phase of CPCR. Notably, no studies are published that even address this topic. Given the potential adverse impact of corticosteroid use demonstrated in other clinical situations (e.g., head trauma), it must be clearly demonstrated that steroid use in this phase of CPCR does not pose an increased risk of adverse outcome.

The data suggesting a neutral or ineffective effect of corticosteroid use during the ALS phase of CPCR is limited to a single human RCT (Paris 1984; LOE 6, fair). This study demonstrated that survival to ICU admission in patients suffering out-of-hospital arrest was no different for those patients given saline vs corticosteroid. No patient in this study survived to hospital discharge. While this study was well-designed, its relatively small sample size (n=86) and evaluation only of patients with pulseless idioventricular rhythm with CPCR started in the prehospital setting limit the conclusion that steroid use is not beneficial.

The data supporting a beneficial effect of corticosteroid use during the ALS phase of CPCR, although limited, is promising. The earliest suggestion of benefit in people was published in the late 1970s by the same group (White 1976, White 1979). The initial case series of 5 patients (White 1976; LOE 6, poor) purported a benefit of steroids as a rescue therapy, but had so many confounders as to make solid conclusions impossible. The group's follow on retrospective study (White 1979; LOE 6, fair) of patients with pulseless idioventricular rhythm did have a fair sample size (n=458), but the study design and use of multiple drugs in addition to corticosteroids makes it impossible to clearly delineate a positive effect of steroid use, although authors cite significant improvement in ROSC rate (52%) compared to patients not receiving steroids. The earliest study of steroid use in a veterinary target species was published in 1993 (Smithline 1993; LOE 3, fair). This experimental RCT in rats was well-designed and demonstrated significantly higher resuscitation rate in rats given 0.25 mg hydrocortisone (92%) during CPCR compared to placebo (50%) or a lower dose of hydrocortisone (50%). Results also showed a trend for shorter-duration CPCR and lower overall dose of epinephrine to achieve ROSC. A subsequent human trial (Tsai 2007; LOE 6, poor) demonstrated significant improvement in ROSC overall for patients given hydrocortisone at any point during CPCR, and in a subset of patients given hydrocortisone within 6 minutes of ED arrival, compared to patients not given steroids. However, this trial's poor study design (nonrandomized, open-label, significant patient selection bias), relatively small sample size (n=97), and evaluation only of patients treated for non-traumatic out-of-hospital arrest limits unequivocal conclusions. The most recent human RCT (Mentzelopoulos 2009; LOE 6, poor) demonstrated improved ROSC and survival in patients given corticosteroids (methylprednisolone) compared to vasopressin, with open-label epinephrine permitted. The relatively small sample size (n=100) and poor study design do not allow clear delineation of the individual effect of corticosteroid administration vs other drugs, as vasopressin or epinephrine or both were given to patients. Furthermore, the data do not permit one to clearly delineate if improved survival was due to corticosteroids given during arrest or in the post-resuscitation phase, as one arm of the study used hydrocortisone in the post-resuscitation phase. Finally, the most recent veterinary study (Hofmeister 2009; LOE 4, fair) to report a possible beneficial effect of corticosteroid use suggests a significant positive impact of steroid use during ALS phase of CPCR. Of the 7 dogs in this retrospective review of patients treated for CPA at a university teaching hospital, the odds ratio for likelihood of achieving

ROSC in patients treated with corticosteroids was 272, which was statistically significant. However, only 7/204 patients (3%, all dogs) received corticosteroids during CPCR, and all dogs were given more than 2 drugs during resuscitation, thus confounding the ability to determine the true effect of corticosteroids. A further significant limitation to conclusions made by the authors was that timing of administration of steroids (i.e., before ROSC was achieved vs after) was not confirmed.

Conclusion: Unequivocal data to support or refute a beneficial effect of corticosteroid use during the ALS phase of CPCR is lacking, and thus use of steroids during this phase of CPCR cannot be recommended. However, sufficient data exists that use of steroids is possibly beneficial to justify efforts through well-designed clinical trials for further research. A developing body of evidence, evaluating relative adrenal insufficiency in patients during and after CPA, strongly suggests a positive effect on outcome with the use of corticosteroids (not examined in this review) administered during the PLS phase of CPCR; directed efforts to evaluate steroid use during this phase are particularly warranted.

7. Conclusion

DISCLAIMER: Potential possible wording for a Consensus on Science Statement. Final wording will differ due to other input and discussion.

CONSENSUS ON SCIENCE:

There is scarce data specifically evaluating the effect of corticosteroids administered during the ALS phase of cardiopulmonary-cerebral resuscitation in veterinary patients. A single small RCT in people (Paris 1984, LOE 6) did not show any benefit with use of corticosteroids. Very limited data in animals (Hofmeister 2009, LOE 4; Smithline 1993, LOE 3) and in people (Mentzelopoulos 2009, LOE 6; Tsai 2007, LOE 6), albeit from studies with significant constraints or from retrospective reviews, appear to support possible benefit from corticosteroid administration.

8. Acknowledgement

N/A

9. Citation list

Hofmeister EH, Brainard BM, Egger CM, Kang S. Prognostic indicators for dogs and cats with cardiopulmonary arrest treated by cardiopulmonary cerebral resuscitation at a university teaching hospital. J Am Vet Med Assoc 2009;235:50-7.

OBJECTIVE: To determine the association among signalment, health status, other clinical variables, and treatments and events during cardiopulmonary cerebral resuscitation (CPCR) with the return of spontaneous circulation (ROSC) for animals with cardiopulmonary arrest (CPA) in a veterinary teaching hospital.
DESIGN: Cross-sectional study.
ANIMALS: 161 dogs and 43 cats with CPA.
PROCEDURES: Data were gathered during a 60-month period on animals that had CPA and underwent CPCR. Logistic regression was used to evaluate effects of multiple predictors for ROSC.
RESULTS: 56 (35%) dogs and 19 (44%) cats had successful CPCR. Twelve (6%) animals (9 dogs and 3 cats) were discharged from the hospital. Successfully resuscitated dogs were significantly more likely to have been treated with mannitol, lidocaine, fluids, dopamine, corticosteroids, or vasopressin; had CPA while anesthetized; received chest compressions while positioned in lateral recumbency; and had a suspected cause of CPA other than hemorrhage or anemia, shock, hypoxemia, multiple organ

dysfunction syndrome, cerebral trauma, malignant arrhythmia, or an anaphylactoid reaction and were less likely to have been treated with multiple doses of epinephrine, had a longer duration of CPA, or had multiple disease conditions, compared with findings in dogs that were not successfully resuscitated. Successfully resuscitated cats were significantly more likely to have had more people participate in CPCR and less likely to have had shock as the suspected cause of CPA, compared with findings in cats that were not successfully resuscitated.
CONCLUSIONS AND CLINICAL RELEVANCE: The prognosis was grave for animals with CPA, except for those that had CPA while anesthetized.

Mentzelopoulos SD, Zakynthinos SG, Tzoufi M, Katsios N, Papasthlianou A, Gkisioti S, Stathopoulos A, Kollintza A, Stamataki E, Roussos C. Vasopressin, epinephrine, and corticosteroids for in-hospital cardiac arrest. Arch Intern Med 2009;169:15-24.

BACKGROUND: Animal data on cardiac arrest showed improved long-term survival with combined vasopressin-epinephrine. In cardiac arrest, cortisol levels are relatively low during and after cardiopulmonary resuscitation. We hypothesized that combined vasopressin-epinephrine and corticosteroid supplementation during and after resuscitation may improve survival in refractory in-hospital cardiac arrest.
METHODS: We conducted a single-center, prospective, randomized, double-blind, placebo-controlled, parallel-group trial. We enrolled 100 consecutive patients with cardiac arrest requiring epinephrine according to current resuscitation guidelines. Patients received either vasopressin (20 IU per cardiopulmonary resuscitation cycle) plus epinephrine (1 mg per resuscitation cycle) (study group; n = 48) or isotonic sodium chloride solution placebo plus epinephrine (1 mg per resuscitation cycle) (control group; n = 52) for the first 5 resuscitation cycles after randomization, followed by additional epinephrine if needed. On the first resuscitation cycle, study group patients received methylprednisolone sodium succinate (40 mg) and controls received saline placebo. Postresuscitation shock was treated with stress-dose hydrocortisone sodium succinate (300 mg daily for 7 days maximum, with gradual taper) (27 patients in the study group) or saline placebo (15 patients in the control group). Primary end points were return of spontaneous circulation for 15 minutes or longer and survival to hospital discharge.
RESULTS: Study group patients vs controls had more frequent return of spontaneous circulation (39 of 48 patients [81%] vs 27 of 52 [52%]; P = .003) and improved survival to hospital discharge (9 [19%] vs 2 [4%]; P = .02). Study group patients with postresuscitation shock vs corresponding controls had improved survival to hospital discharge (8 of 27 patients [30%] vs 0 of 15 [0%]; P = .02), improved hemodynamics and central venous oxygen saturation, and more organ failure-free days. Adverse events were similar in the 2 groups.
CONCLUSION: In this single-center trial, combined vasopressin-epinephrine and methylprednisolone during resuscitation and stress-dose hydrocortisone in postresuscitation shock improved survival in refractory in-hospital cardiac arrest.

Paris PM, Stewart RD, Deggler F. Prehospital use of dexamethasone in pulselsess idioventricular rhythm. Ann Emerg Med 1984;13:1008-10.

We investigated the prehospital use of 100 mg dexamethasone for the treatment of cardiac arrest patients with pulseless idioventricular rhythms (PIVR). In the 86 patients studied in this prospective, randomized, double-blind investigation, four of the 46 patients receiving saline and two of the 37 patients receiving dexamethasone survived long enough to be admitted to the hospital intensive care unit. There were no long-term survivors. No benefit from the field use of 100 mg dexamethasone in PIVR could be identified in this study.

Smithline H, Rivers E, Appleton T, Nowak R. Corticosteroid supplementation during cardiac arrest in rats. Resuscitation 1993;25:257-64.

HYPOTHESIS: Corticosteroids will improve the rate of resuscitation from cardiac arrest.
DESIGN: Prospective blinded randomized placebo-controlled trial.
INTERVENTION: An 8-min cardiac arrest was induced by KCl infusion and chest restriction in 36 male Sprague-Dawley rats with continuous EKG and arterial blood pressure monitoring. At the start of CPR the rats received one of three study drugs: normal saline (placebo); 0.05 mg hydrocortisone (Group A) and 0.25 mg hydrocortisone (Group B). Mechanical ventilation, chest compressions and ACLS drug administration were provided following a standardized algorithm.
RESULTS: The resuscitation rate was significantly higher ($P < 0.05$) in Group B (92%) compared to Group A (50%) and placebo (50%). For the rats resuscitated, the duration of CPR (placebo = 163 s, Group A = 126 s, Group B = 120 s) and the amount of epinephrine used (placebo = 0.007 mg, Group A = 0.005 mg, Group B = 0.005 mg) did not reach statistical significance ($P = 0.15$ and $P = 0.21$).
CONCLUSION: Hydrocortisone significantly increased the rate of ROSC from cardiac arrest. There also appears to be a trend of decreasing duration of CPR and epinephrine requirements with hydrocortisone. Further studies evaluating the mechanism of action and long term effects of hydrocortisone in cardiac arrest need to be conducted.

Tsai MS, Huang CH, Chang WT, Chen WJ, Hsu CY, Hsieh CC, Yang CW, Chiang WC, Ma MH, Chen SC. The effect of hydrocortisone on the outcome of out-of-hospital cardiac arrest patients: a pilot study. Am J Emerg Med 2007;25:318-25.

OBJECTIVE: Several studies have disclosed the importance of serum adrenocorticotropic hormone and cortisol levels in resuscitation. The objective of this study was to observe the effect of hydrocortisone on the outcome of out-of-hospital cardiac arrest (OHCA) patients.
DESIGN: Prospective, nonrandomized, open-labeled clinical trial.
SETTING: Emergency department (ED) of National Taiwan University Hospital.
PATIENTS AND PARTICIPANTS: Ninety-seven nontraumatic adult OHCA victims.
INTERVENTIONS: Serum adrenocorticotropic hormone and total cortisol levels were examined in all patients. The hydrocortisone group (n = 36) received 100 mg intravenous hydrocortisone during resuscitation, and the nonhydrocortisone group (n = 61) received 0.9% saline as placebo.
MEASUREMENTS AND RESULTS: Comparison of return of the spontaneous circulation (ROSC) rates between the 2 groups was analyzed. The hydrocortisone group had a significantly higher ROSC rate than the nonhydrocortisone group (61% vs 39%, P = .038). Hydrocortisone administration within 6 minutes after ED arrival led to an increased ROSC rate (90% vs 50%, P = .045). The hydrocortisone and nonhydrocortisone groups did not differ in the development of electrolyte disturbances, gastrointestinal tract bleeding, or infection during early postresuscitation period (gastrointestinal bleeding: 41% vs 46%, P = .89; infection: 50% vs 75%, P = .335). There was no significant difference between the hydrocortisone and nonhydrocortisone groups in terms of 1- and 7-day survival and hospital discharge rates.
CONCLUSIONS: Hydrocortisone treatment during resuscitation, particularly when administrated within 6 minutes of ED arrival, may be associated with an improved ROSC rate in OHCA patients.

White BC. Pulseless idioventricular rhythm during CPR: an indication for massive intravenous bolus glucocorticoids. J Am Coll Emerg Phys 1976;5:449-54.

Five consecutive patients were initially resuscitated successfully from pulseless idioventricular rhythm with the use of 100 mg of dexamethasone administered by intravenous push after all conventional modes of management had failed. In this small series, two of the five patients are long-term survivors and the deaths of the other three patients are attributable to advanced underlying pathology. The

possible mechanisms of action of the glucocorticoids are not conclusively known. There is a need for detailed laboratory study of Purkinje conduction and single-cell depolarization and mechanical patterns, under controlled settings approximating the clinical conditions.

White BC, Petinga TJ, Hoehner PJ, Wilson RF. Incidence, etiology, and outcome of pulseless idioventricular rhythm treated with dexamethasone during advanced CPR. J Am Coll Emerg Phys 1979;8:188-93.

The cardiac resuscitation records of 458 patients who received advanced cardiac life support at Detroit General Hospital during the last two years were reviewed to identify patients who had pulseless idioventricular rhythm (PIVR) recognized and treated with dexamethasone. Twenty-five cases were identified. The initial successful resuscitation rate of 52% in these patients contrasts sharply with other published data indicating 100% failure with the use of conventional chronotropic drugs. The most common etiology of cardiac arrest in our patients who display PIVR during resuscitation is hypoperfusion shock. Dexamethasone may counteract the lethal arrhythmia by causing the release of aditional adenosine triphosphate into the cytoplasm from the mitochondria.