WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care

Worksheet author(s)

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Clinical question.

In adult patients with ROSC after cardiac arrest (prehospital or in-hospital) (P), does treatment with corticosteroids (I) as opposed to standard care (C), improve outcome (O) (eg. survival)?

Is this question addressing an intervention/therapy, prognosis or diagnosis? Intervention/therapy
State if this is a proposed new topic or revision of existing worksheet: New topic

Conflict of interest specific to this question

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? No

Search strategy (including electronic databases searched).

Cochrane Library search:
("Heart Arrest"[Mesh] OR "Cardiopulmonary Resuscitation"[Mesh]) AND ("Pituitary-Adrenal System"[Mesh] OR "Adrenal Insufficiency"[Mesh] OR "Adrenal Cortex Hormones"[Mesh] OR "Glucocorticoids"[Mesh] OR "Hydrocortisone"[Mesh] OR "Cortisone"[Mesh] OR "Prednisolone"[Mesh] OR "Prednisone"[Mesh] OR "Methylprednisolone"[Mesh] OR "Dexamethasone"[Mesh] OR "Betamethasone"[Mesh]). 5 results.

PubMed search:
("Heart Arrest"[Mesh] OR "Cardiopulmonary Resuscitation"[Mesh]) AND ("Pituitary-Adrenal System"[Mesh] OR "Adrenal Insufficiency"[Mesh] OR "Adrenal Cortex Hormones"[Mesh] OR "Adrenal Cortex Hormones "[Pharmacological Action] OR "Glucocorticoids"[Mesh] OR "Hydrocortisone"[Mesh] OR "Cortisone"[Mesh] OR "Prednisolone"[Mesh] OR "Prednisone"[Mesh] OR "Methylprednisolone"[Mesh] OR "Dexamethasone"[Mesh] OR "Betamethasone"[Mesh]). 184 results.

EMBASE search:
('heart arrest'/exp/mj OR 'resuscitation'/exp/mj) AND 'corticosteroid'/exp/mj
347 results.

AHA Endnote database search: (“arrest” OR “CPR”) AND (“adrenal” OR “glucocorticoids” OR ”steroid” OR “hydrocortisone” OR “cortisone” OR “prednisolone” OR “prednisone” OR “methylprednisolone” OR “dexamethasone” OR “betamethasone”): 379 results.

Titles and abstracts (where appropriate) of all results were examined for relevance. Where doubt existed the full papers were reviewed to identify relevant papers.

The reference lists of relevant papers were searched for other relevant papers.

Forward searching of relevant papers was performed using SCOPUS.

- State inclusion and exclusion criteria

Exclusion criteria:
Treatment with corticosteroids pre-arrest
Treatment with corticosteroids during cardiac arrest (to improve ROSC rate)
Models which used prolonged maintenance on cardiopulmonary bypass / cardioplegia, isolated perfused organs, carotid artery occlusion, deep hypothermic circulatory arrest

- Number of articles/sources meeting criteria for further review:

5 studies met the criteria for further review. Of these, two were LOE 2 (non-randomised with concurrent controls) and three were LOE 5 (two used animal models, one was a small single-centre randomised controlled trial that did not directly address the clinical question).

Summary of evidence

Evidence Supporting Clinical Question

Good					
Fair					
Poor					
	1	**2**	**3**	**4**	**5**
Level of evidence					

A = Return of spontaneous circulation
B = Survival of event
C = Survival to hospital discharge
D = Intact neurological survival
E = Other endpoint
Italics = Animal studies

Evidence Neutral to Clinical question

Good					
Fair		Jastremski 1989 D			
Poor		Grafton 1988 CE			Mentzelopoulos 2009, AC *Ebmeyer 2000, E* *Katz, 1989, E*
	1	**2**	**3**	**4**	**5**
Level of evidence					

A = Return of spontaneous circulation
B = Survival of event
C = Survival to hospital discharge
D = Intact neurological survival
E = Other endpoint
Italics = Animal studies

Evidence Opposing Clinical Question

Good					
Fair					
Poor					
	1	**2**	**3**	**4**	**5**
Level of evidence					

A = Return of spontaneous circulation
B = Survival of event
C = Survival to hospital discharge
D = Intact neurological survival
E = Other endpoint
Italics = Animal studies

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

Five studies have investigated the use of corticosteroids post ROSC. Two of these (Ebmeyer, Katz) were animal studies. Two of the human studies (Grafton, Jastremski) were non-randomised and one (Mentzelopoulos) was a randomised controlled trial of a package of care that included vasopressin and dexamethasone during cardiac arrest and hydrocortisone post cardiac arrest. None of these studies provide good evidence on which to make decisions about whether steroids provide benefit in this situation.

Ebmeyer used a dog cardiac arrest model. They provided a package of care consisting of thiopental/phenytoin/methylprednisolone plus hypothermia (6 dogs) and compared the outcomes with a control group that had hypothermia alone (6 dogs). However, the two groups had different periods of hypothermia, different blood pressure control and different glucose control. Multiple outcomes were measured. Some of these were improved in the group receiving the package of care, but it is impossible to tease out what effect methylprednisolone had. A statistical summary has not been produced because interpretation would be impossible.
Katz used a rat model. One group (5 rats) received methylprednisolone following cardiac arrest and was compared to another group (5 rats) receiving placebo. Outcomes were measured at just 20 mins following arrest. There was a reported reduction in the use of epinephrine (reported mean+/-SD as 0.06+/-0.04 mg in treatment group vs. 0 in treatment group, calculated p=0.010 using a standard t-test, p=0.029 using Welch's t test for unequal variance) and an increase in the number of rats with EEG activity post arrest (1/5 in control group vs. 5/5 in the methylprednisolone group, calculated p=0.048 using Fisher's exact test) though no statistical analysis of these were reported in the paper. Brain cytosolic and lysosomal enzymes were measured and showed variable results. Due to the short follow-up, the small group sizes and the lack of functional outcome measure, this study also provides little evidence for or against the use of steroids post ROSC.

The two human studies non-randomised studies (Grafton, Jastremski) were also limited. They both compared the outcomes of patients who received steroids with those that did not. Both used logistic regression to attempt to control for confounding factors.

Grafton performed a retrospective notes review on 459 consecutive patients admitted after out-of-hospital cardiac arrest and compared the outcome of those who received steroids with those who did not. The outcomes used were "awakening" and survival to hospital discharge. Logistic regression was used to account for seven potential confounding factors. 389 patients were "not awake on admission". 77 records were incomplete. For all patients with complete records, using awakening as the outcome measure, the odds ratio for never regaining consciousness for those who had steroids was 1.18 (95%CI 0.83-1.61, p>>0.05). For the group of patients "not awake on admission" with complete records, again using awakening as the outcome measure, the odds ratio for never regaining consciousness for those who had steroids was 1.18 (95%CI 0.85-1.61, p>>0.05). The results of logistic regression using survival to hospital discharge as the outcome measure are not reported.
The results of this study depend on whether any other potential confounding factors exist that were not controlled for. This seems likely as steroids were given for "lung disease, usually aspiration" in 31% cases. Aspiration is likely to have been related to outcome (being associated with worse outcome) so satisfies the definition of a confounding factor, though was not used as a variable in the logistic regression analysis. This alone calls into question the results of the analysis.

Jastremski performed a retrospective sub-group analysis on patients in the BRCT1 trial. This was a trial of 262 patients with severe global ischaemic cerebral insults, in most cases due to cardiac arrest, with no purposeful response to pain 10-50 mins following cardiac arrest. In the BRCT1 trial patients were randomised to receive thiopental sodium or placebo. Steroid use was at the discretion of treating clinicians. Outcomes (mortality and recovery of cerebral function) were evaluated at 48 to 72 hrs, 10 days and 1, 3, 6 and 12 months post-arrest. One-year mortality and best cerebral recovery (measured using the cerebral performance category) achieved at any time were reported.
Univariate analysis failed to show any benefit from steroid use: one-year mortality in the steroid group was 145/191 vs. 60/70 in the no-steroid group (p=0.09 using chi-squared test), and good cerebral recovery (CPC 1 or 2) at any time occurred in 65/191 in the steroid group vs. 24/70 in the no-steroid group (p=0.97 using chi-squared test). Multivariate analysis (logistic regression) was then used to attempt to control for baseline differences between the steroid and no-steroid groups using variables related to steroid use and variables known to affect outcome. Use of steroids was not associated with improvements in either mortality or good neurological outcome. This study is again limited by the potential for unknown confounding factors to be present, and even the known confounders may not have been fully controlled for.

Mentzelopoulos performed a single-centre randomised controlled trial in patients who had in-hospital cardiac arrest and required epinephrine. The study group received dexamethasone (40mg) and vasopressin (20IU per cardiopulmonary resuscitation cycle) in addition to epinephrine and the control group received isotonic sodium chloride placebo in addition to epinephrine. Postresuscitation shock was treated in the study goup with hydrocortisone (300mg daily) and with saline placebo in the control group. The study group had more frequent ROSC (39/48 vs. 27/52, p=0.003) and survival to hospital discharge (8/27 vs. 0/15, p=0.02).
This trial demonstrates significant benefit from the package of care, though it is impossible to know whether it was due to the vasopressin, the dexamethasone, the hydrocortisone or some combination of them. However, the total number of patients in the trial was relatively small. It is extremely important that the study and control groups did not have any baseline differences as just a few

extra deaths in the control group could have influenced the results significantly though no obvious imbalances are seen in the publication. It is also important to emphasize that it consists of patients with in-hospital arrests only, with a very low number of initial VF, only 13 and 15%. Although the internal validity of the trial appears to be relatively good, it does not provide good quality evidence about the clinical question posed by this worksheet so has been given a quality score of Poor.

Acknowledgements:
Nil

Citation List

Ebmeyer U., Safar P., Radovsky A., Xiao F., Capone A., Tanigawa K., Stezoski S.W. Thiopental combination treatments for cerebral resuscitation after prolonged cardiac arrest in dogs. Exploratory outcome study. Resuscitation. 2000 Jul;45(2):119-31.

Level of evidence 5 (Non-randomised animal study). Neutral for steroid use. Quality score: Poor (control group inadequate).
Investigated the benefit of adding thiopental, phenytoin and methylprednisolone to mild hypothermia in a dog model of cardiac arrest. Important comparison is group 2 (hypothermia) with group 4 (hypothermia plus thiopental/phenytoin/methylprednisolone) Comparison groups defined. Outcomes defined. Method of outcome determination blinded and the same in all groups. Functional outcome measured using two scores: the overall performance category (OPC) and the neurological deficit score (NDS). As there should be few differences between groups in baseline characteristics control of confounding should not be necessary. Follow up to 96 hours. Histological outcome evaluated after 96 hours.
Results neutral: Although there was significant improvement in OPC score with thiopental/phenytoin/methylprednisolone there was no significant improvement in NDS. Significant improvement in histologic damage score with thiopental/phenytoin/methylprednisolone but histologic damage scores only done on 3 of the 6 brains of animals in group 4 due to errors in post-mortem handling of the specimens.
Major problems:

1. the differences between treatment of Groups 2 and 4 : Group 4 had hypothermia for twelve hours, Group 2 had it for two hours, Group 4 received controlled mild hypertension for the first 4 hours post arrest, Group 2 did not, and Group 4 had higher blood glucose than group 2 (255 +/- 57 vs. 235 +/- 37) i.e. inadequate control group.
2. the inability to separate the effects of thiopental, phenytoin and methylprednisolone (they were given together as a package of care).

Funding: AS Laerdal Foundation and US Navy Medical Research and Development Command

Grafton S.T., Longstreth Jr. W.T. Steroids after cardiac arrest: A retrospective study with concurrent, nonrandomized controls. Neurology 1988; 38(8): 1315-1316

Level of evidence 2 (Non-randomised study, concurrent controls). Neutral for steroid use (no benefit or harm). Quality score: Poor
Comparison groups defined, Outcomes defined: “awakening” and survival to hospital discharge. Method of outcome determination the same in both groups, but determination of “awakening” not blinded and not objective (notes review). Some potential confounders formally identified and controlled for using logistic regression, but other potential confounders not controlled for (e.g. steroids given for “lung disease, usually aspiration” in 31% cases but aspiration not controlled for in the logistic regression analysis). Follow up to hospital discharge. Completeness poor: notes of 6 patients could not be found, 76 other patients had missing data and were excluded from the analysis.
NB Analysis reports results for all 458 patients admitted following out of hospital cardiac arrest and also for the 389 patients who were “not awake on admission”
No comment on funding.

Jastremski M., Sutton-Tyrrell K., Vaagenes P., Abramson N., Heiselman D., Safar P., the Brain Resuscitation Clinical Trial 1 Study Group. Glucocorticoid treatment does not improve neurological recovery following cardiac arrest. Journal of the American Medical Association 1989; 262(24): 3427-3430

Level of evidence 2 (Non-randomised study, concurrent controls). Neutral for steroid use (no benefit or harm). Quality score: Fair

Retrospective sub-group analysis of patients in another study (BRCT1). The BRCT1 trial randomised patients to receive standard care or standard care plus 30 mg/kg thiopentone within 50 mins of ROSC. Use of steroids was at the discretion of individual physicians.
Comparison groups were defined, and outcomes were defined and objective: mortality and recovery of cerebral function (CPC 1 and 2=good cerebral recovery, CPC 3 and 4=poor recovery). Method of outcome determination was the same in both groups, but was not blinded (see report in Am J Emerg Med 1986; 4: 72-86). Outcomes were evaluated at 48 to 72 hrs, 10 days and 1, 3, 6 and 12 months post-arrest. One-year mortality and best cerebral recovery achieved at any time were reported. The association between baseline variables and steroid use was reported, to investigate potential confounders. Logistic regression was said to control for "all known factors that might have independently influenced outcome" and the factors controlled for were listed. There was no sensitivity analysis to investigate other potential confounding factors. The use of steroids was not a significant predictor of mortality or good neurological outcome but details of odds ratios and p values were not reported.
To assess interaction between steroids and thiopentone, the outcome of using steroids in the thiopentone and control groups were assessed separately and "failed to show any benefits from steroid treatment" though the analysis is again not detailed.
To investigate whether differences between sites in their use of steroids had any effect (i.e. whether confounding by indication was occurring) sites were grouped as low-use, moderate-use or high-use. Mortality and the incidence of good cerebral outcome were reported for each of these groups. No significant differences were found in either outcome related to frequency of steroid use. However, the size of the groups was not reported (so the analysis was possibly underpowered) and the analysis appears to have been univariate rather than multivariate.
There was no significant difference in incidence of infection or infection-associated mortality between patients receiving steroids and those not receiving steroids. There does not appear to be any evidence for the statement made in the abstract that "…glucocorticoids…may be associated with serious complications…"
Completeness: only 1 patient excluded, who had been given both dexametasone and methylprednisolone.
Funding: NIH

Katz L., Vaagenes P., Safar P., Diven W. Brain enzyme changes as markers of brain damage in rat cardiac arrest model. Effects of corticosteroid therapy. Resuscitation 1989; 17(1): 39-53

Level of evidence 5 (animal study). Neutral (no statistically significant benefit) for steroid use. Quality score: Poor
Comparison groups were defined: dexamethasone given immediately after ROSC in group IV, and compared to control group II receiving placebo post ROSC. Follow-up: 20 mins post cardiac arrest.
Outcomes were defined: clinical variables and cytosolic and lysosomal enzymes were compared between groups. The post cardiac arrest methylprednisolone group (IV) had a lower epinephrine requirement and increased incidence of return of EEG than the placebo group (III) though statistical significance was not reported. There were variable effects on different enzymes.
The study had a control group but due to the short follow-up, the small group sizes and the lack of functional outcome measure, this study provides poor evidence of benefit from steroids post ROSC.
Funding: Upjohn Company, Kalamazoo, Michigan and the AS Laerdal Foundation

Mentzelopoulos S., Zakynthinos S., Tzoufi M., Katsios N., Papastylianou A., Gkisioti S., Stathopoulos A., Kollintza A., Stamataki E. Vasopressin, epinephrine, and corticosteroids for in-hospital cardiac arrest. Archives of Internal Medicine 2009; 169(1): 15-24

Level of Evidence: 5 (RCT, but did not directly address clinical question) Quality score: Poor for answering the clinical question.
This is a relatively small, single-centre RCT. Only in-hospital arrests were studied with a very low number of initial VF, only 13 and 15% in the groups. It does not directly address the question of whether corticosteroids improve outcome after cardiac arrest. The study group received dexamethasone and vasopressin during the arrest and hydrocortisone post arrest if they had postresuscitation shock. It is impossible to determine whether the benefits seen in the trial were due to the addition of vasopressin and/or dexamethasone and/or the hydrocortisone. Neutral for steroid use because of this (though supportive for the whole package of vasopressin/dexamethasone/hydrocortisone in addition to usual epinephrine).
Funding: Thorax Research Foundation, Athens, Greeceand the Greek Society of Intensive Care Medicine