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

Worksheet author(s)

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Clinical question.

In adult cardiac arrest (asystole, pulseless electrical activity, pulseless VT and VF) (prehospital [OHCA], in-hospital [IHCA]) (P), does the use of steroid or hormonal therapy (estrogen, progesterone, hydrocortisone, insulin, growth factor etc) alone or combination with other drugs (I) compared with not using drugs (or a standard drug regimen) (C), improve outcomes (eg. ROSC, survival) (O).

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

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).

PubMed "heart arrest" or "cardiac arrest" as MESH (headings) AND "corticosteroids or hydrocortisone or prednisone or prednisolone or methylprednislone or dexamethasone" textword in abstract.
Ovid search using key words "heart arrest" AND "cardiac arrest" AND "corticosteroids or hydrocortisone or prednisone or prednisolone or methylprednislone or dexamethasone"
EMBASE search using text words (all fields) "heart arrest" or "cardiac arrest" AND "corticosteroids or hydrocortisone or prednisone or prednisolone or methylprednislone or dexamethasone"
Cochrane database for systematic reviews, Google Scholar.

PubMed ""heart arrest" or "cardiac arrest" as MESH (headings) AND "estrogen or oestrogen or estradiol or oestrodiol" textword in abstract.
Ovid search using key words "heart arrest" AND "cardiac arrest" AND "estrogen or estrogen or oestrogen or estradiol or oestrodiol"
EMBASE search using text words (all fields) "heart arrest" or "cardiac arrest" AND "estrogen or oestrogen or estradiol or oestrodiol"
Cochrane database for systematic reviews, Google Scholar.

PubMed ""heart arrest" or "cardiac arrest" as MESH (headings) AND "progesterone or progestogen " textword in abstract.
Ovid search using key words "heart arrest" AND "cardiac arrest" AND "progesterone or progestogen"
EMBASE search using text words (all fields) "heart arrest" or "cardiac arrest" AND "progesterone or progestogen"
Cochrane database for systematic reviews, Google Scholar.

PubMed ""heart arrest" or "cardiac arrest" as MESH (headings) AND "insulin" textword in abstract.
Ovid search using key words "heart arrest" AND "cardiac arrest" AND "insulin"
EMBASE search using text words (all fields) "heart arrest" or "cardiac arrest" AND "insulin"
Cochrane database for systematic reviews, Google Scholar.

PubMed ""heart arrest" or "cardiac arrest" as MESH (headings) AND "insulin-like growth factor" textword in abstract.
Ovid search using key words "heart arrest" AND "cardiac arrest" AND "insulin-like growth factor"
EMBASE search using text words (all fields) "heart arrest" or "cardiac arrest" AND "insulin-like growth factor"
Cochrane database for systematic reviews, Google Scholar.

PubMed ""heart arrest" or "cardiac arrest" as MESH (headings) AND "growth hormone" textword in abstract.
Ovid search using key words "heart arrest" AND "cardiac arrest" AND "growth hormone"
EMBASE search using text words (all fields) "heart arrest" or "cardiac arrest" AND "growth hormone"
Cochrane database for systematic reviews, Google Scholar.

1.heart arrest .mp or Heart Arrest/
2. cardiac arrest .mp
3. (steroid or corticosteroid or hydrocortisone or prednisone or prednisolone or methylprednisolone or dexamethasone).mp or (Steroids or corticosteroids or hydrocortisone or prednisone or prednisolone or methylprednisolone or dexamethasone)/
4. (estrogen or oestrogen or estradiol or oestradiol).mp or (estrogen or or oestrogen or estradiol or oestrodiol)/
5. (progesterone or progestogen).mp or (progesterone or progestogen)/
6. hydrocortisone.mp or hydrocortisone/
7. insulin/ or insulin-like growth factor I/ or insulin .mp or insulin-like growth factor II/
8. growth factor .mp
9. growth hormone .mp

10. 1 or 2
11. 3 and 10
12. 4 and 10
13. 5 and 10
14. 6 and 10
15. 7 and 10
16. 8 and 10
17. 9 and 10
18. 11 or 12 or 13 or 14 or 15 or 16 or 17

1095 articles

19. Limit 18 to (human OR animal) AND (clinical trial)

89 articles

• State inclusion and exclusion criteria

Inclusion: All human or animal studies evaluating one of the listed therapies in cardiac arrest were included where a clinical outcome (ROSC or mortality or neurological function) is one of the endpoints of the study

Exclusion: Studies which looked at therapy post cardiac arrest [as opposed to intra-cardiac arrest] were excluded as these are examined in a separate worksheet. Additionally, one study was excluded because it was published in abstract form but never in a manuscript.

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

Of all databases searched and references of relevant articles, 6 studies met criteria for further review. Of these, two were LOE 1 (RCTs), one LOE 2 (non-randomized, concurrent controls), no LOE 3 (retrospective controls), two LOE 4 (no controls), and one LOE 5 (animal studies).

Summary of evidence

Evidence Supporting Clinical Question

Good					
Fair				**White (A)**	***Smithline (A)***
Poor	**Mentzelopoulos (A,C, E)**	**Tsai (A)**			
	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					
Poor				**White (A)**	
	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	**Paris (A)**				
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:

We divided the clinical question "steroid or hormonal therapy" into components, looking separately at corticosteroids (including prednisone, prednisolone, methylprednisolone, hydrocortisone, dexamethasone), estrogens (including estrogen, oestrogen, estrodiol, oestrodiol), progesterone/progestagen, insulin (insulin, glucose-insulin-potassium, GIK), and growth factors (insulin-like growth factor, ILGF, growth hormone). Addressing each of these:

Corticosteroids: The interest in the use of steroids during cardiac arrest originated in the 1970s after the report of a very small case series of survivors of arrest who had received corticosteroids as rescue therapy. (LOE 4, poor White 1976) This report was followed by a larger retrospective analysis by the same investigator who concluded that corticosteroid administration in the intra-arrest period was associated with improved ROSC and survival in a small number of patients. (LOE 4, poor White 1979)These observational data and retrospective observations were tested in a small randomized, blinded human trial which did not find any difference in ROSC in patients receiving steroids versus placebo. (Paris 1984) However, the quality of this trial is limited by small sample size and the very high mortality rate.

A single animal study (LOE 5, Fair Smithline H, 1993) compared two doses of hydrocortisone with placebo, after 8 minutes of experimental cardiac arrest in rats. There was an improved rate of ROSC in the higher dose group. A single center unrandomised human pilot study (LOE 2, poor Tsai MS, 2007) compared 100mg hydrocortisone with placebo in out-of-hospital CA patients. There was an improvement in ROSC in the hydrocortisone group but no improvement in 1 or 7 day survival, and poor neurological function in survivors. This non-randomized study had several flaws mostly related to the open-label design and patient selection. (Tsai MS 2007) The study was open-label with enrollment based on real-time consent of the family to provide the drug – if the family consented, then open-label drug was given. If not or if family was not present, then patient was given placebo. The resultant enrollment was lopsided with 36 patients in the hydrocortisone group and 61 in the non-hydrocortisone group.

Most recently, a complex single center in-hospital CA study. (LOE 1, poor Mentzelopoulos SD, 2009) compared vasopressin and methylprednisolone with placebo, with open label epinephrine, and also compared hydrocortisone against placebo in the subset of survivors with postresuscitation shock. There were improvements in ROSC and survival to discharge in the intervention groups. The design was not factorial and it is impossible to determine whether the intra-arrest benefit was due to vasopressin, corticosteroids, or both. This study was self-described as preliminary/pilot in nature with a sample size of 100 patients. The authors are currently conducting a larger-scale prospective randomized trial of similar design. Moreover, it is difficult to know whether the overall mortality benefit is a result of continuous infusion of steroids post-arrest or the intra-arrest interventions. One could postulate from other failed trials of vasopressin that the intra-arrest effect was steroids rather than vasopressin, however there is no way to determine this from the study design itself. The focus of this current analysis is on intra-arrest benefit and a separate worksheet is focused on post-arrest steroid administration. This last study is thus difficult to interpret in light of the multi-medication and multi-pathway design. Overall there are conflicting data on the use of corticosteroids in the intra-arrest period. One rat model RCT suggests potential benefit, one human randomized, placebo-controlled trial found no benefit, one human study of combined therapy is difficult to interpret, and one open-label human study suggested benefit but had poor design.

Finally, there may be a publication bias from work back in the 1980s in that we identified at least one negative randomized trial that was published in abstract form but not in manuscript form (Schwitzer KW: Dexamethasone therapy in bradyasystolic pre-hospital cardiac arrest. Annals of Emergency Medicine 1983; 12:252).

Conclusion: there is evidence of the potential benefits of corticosteroids to inform future human resuscitation research, but insufficient evidence to justify a change in clinical recommendations at present.

Estrogen: It is known that women have fewer episodes of sudden CA than men, and in some studies women have improved outcomes. Estradiol (E2) is possibly neuroprotective in brain injury. No intra-arrest studies done.

Progesterone: There have been no studies of progesterone use in the intra-arrest period.

Insulin: There have been no studies of insulin or glucose-insulin-potassium specifically in the intra-arrest period, though this may be an area for future research.

Insulin-like growth factor or growth hormone: There have been no studies of insulin-like growth factor or growth hormone in the intra-arrest period.

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Citation List

Mentzelopoulos SD, Zakynthinos SG, Tzoufi M, Katsios N, Papastylianou A, Gkisioti S, Stathopoulos A, Kollintza A, Stamataki E, and Roussos C (2009) Vasopressin, epinephrine, and corticosteroids for in-hospital cardiac arrest. Arch Intern Med 169(1): 15-24

Paris PM, Stewart RD, and Deggler F (1984) Prehospital use of dexamethasone in pulseless idioventricular rhythm. Ann Emerg Med 13(11): 1008-10

Smithline H, Rivers E, Appleton T, and Nowak R (1993) Corticosteroid supplementation during cardiac arrest in rats. Resuscitation 25(3): 257-64

Tsai MS, Huang CH, Chang WT, Chen WJ, Hsu CY, Hsieh CC, Yang CW, Chiang WC, Ma MH, and Chen SC (2007) The effect of hydrocortisone on the outcome of out-of-hospital cardiac arrest patients: a pilot study. Am J Emerg Med 25(3): 318-25

White BC, Petinga TJ, Hoehner PJ, and Wilson RF (1979) Incidence, etiology, and outcome of pulseless idioventricular rhythm treated with dexamethasone during advanced CPR. Jacep 8(5): 188-93

White BC (1976) Pulseless idioventricular rhythm during CPR: an indication for massive intravenous bolus glucocorticoids. Jacep 5(6): 449-54

Bibliography of papers used in worksheet with comments

Mentzelopoulos SD, Zakynthinos SG, Tzoufi M, Katsios N, Papastylianou A, Gkisioti S, Stathopoulos A. Kollintza A, Stamataki E, and Roussos C (2009) Vasopressin, epinephrine, and corticosteroids for in-hospital cardiac arrest. Arch Intern Med 169(1): 15-24

Comments: (LOE 1, Poor) This study was self-described as preliminary/pilot in nature with a sample size of 100 patients. The authors are currently conducting a larger-scale prospective randomized trial of similar design. One the main concerns with this investigation is that it is difficult to determine whether the treatment effect resulting in improved ROSC is due to the intra-arrest steroids, vasopressin, or both. Moreover, it is difficult to know whether the overall mortality benefit is a result of continuous infusion of steroids post-arrest or the intra-arrest interventions. One could postulate from other failed trials of vasopressin that the intra-arrest effect was steroids rather than vasopressin, however there is no way to determine this from the study design itself.

Paris PM, Stewart RD, and Deggler F (1984) Prehospital use of dexamethasone in pulseless idioventricular rhythm. Ann Emerg Med 13(11): 1008-10

Comments: (LOE 1, Fair) This randomized, prospective trial is probably the best study of all the citations though still significantly flawed by small sample size. That stated, this study provides no evidence that dexamethasone improved return of spontaneous circulation.

Smithline H, Rivers E, Appleton T, and Nowak R (1993) Corticosteroid supplementation during cardiac arrest in rats. Resuscitation 25(3): 257-64

Tsai MS, Huang CH, Chang WT, Chen WJ, Hsu CY, Hsieh CC, Yang CW, Chiang WC, Ma MH, and Chen SC (2007) The effect of hydrocortisone on the outcome of out-of-hospital cardiac arrest patients: a pilot study. Am J Emerg Med 25(3): 318-25

Comments: (LOE 2, Poor) Open-label with enrollment based on real-time consent of the family to provide the drug – if the family consented, then open-label drug was given. If not or if family was not present, then patient was given placebo. Thus, the concept of "placebo" is unclear and likely ineffective given the design of this investigation. Note that the resultant enrollment was lopsided with 36 patients in the hydrocortisone group and 61 in the non-hydrocortisone group.

White BC (1976) Pulseless idioventricular rhythm during CPR: an indication for massive intravenous bolus glucocorticoids. Journal of the American College of Emergency Physicians 5(6): 449-54

White BC, Petinga TJ, Hoehner PJ, and Wilson RF (1979) Incidence, etiology, and outcome of pulseless idioventricular rhythm treated with dexamethasone during advanced CPR. Jacep 8(5): 188-93

Comments: (LOE 4, Poor) Retrospective, observational and non-randomized so not strong evidence for efficacy of dexamethasone. Moreover, other drugs and other therapies were provided during the arrests in addition to dexamethasone so very unclear as to efficacy.