Clinical question.

"In adult patients with ROSC after cardiac arrest (pre-hospital or in-hospital), does the use of neuroprotective drugs as opposed to standard care improve outcome (eg. Survival with good neurological function)

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).

EMBASE: 'heart arrest'/mj AND 'brain ischemia'/exp AND 'neuroprotection'/ex[
Pubmed: "Heart arrest"[Majr] AND "hypoxia-ischemia, brain"[MESH] AND Neuroprotect* NOT hypotherm
Cochrane database: "cardiac arrest" AND "neuroprotection"
Hand searches of relevant papers for further references.

State inclusion and exclusion criteria

Inclusion: Human trials, either randomized or retrospective, or case series, with contemporaneous or historical controls.
Exclusion: Trials of hypothermia (this is to be evaluated in a separate section); case reports; animal or in vitro models, trials on focal cerebral ischemia (eg ischemic stroke).

Number of articles/sources meeting criteria for further review:

9
## Summary of evidence

### Evidence Supporting Clinical Question

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>A = Return of spontaneous circulation</td>
<td>Reisinger 2009, E</td>
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<td>B = Survival of event</td>
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<td>Aldrete 1981, D</td>
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<td>C = Survival to hospital discharge</td>
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<td>D = Intact neurological survival</td>
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<td>E = Other endpoint</td>
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</tbody>
</table>

*Italics = Animal studies*
## Evidence Neutral to Clinical question

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Evidence</th>
<th>Reason</th>
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<tbody>
<tr>
<td>Fair</td>
<td>Grafton 1988, D Jastremski, 1989, B,D</td>
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</tr>
<tr>
<td>Poor</td>
<td>Monsalve 1987, B, D</td>
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</tr>
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</table>

### 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

<table>
<thead>
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<th>Level of evidence</th>
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<th>Reason</th>
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<tbody>
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<tr>
<td>Fair</td>
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<tr>
<td>Poor</td>
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</tbody>
</table>

### 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
The quest for a neuroprotective drug regimen to prevent hypoxic-ischemic encephalopathy after cardiac arrest has been a long one, but has not been successful. The calcium channel blocker nimodipine was tested in a randomized trial in comatose survivors of out-of-hospital cardiac arrest (Roine, 1990, 3171). There was no overall improvement in survival or neurological outcome (LOE 1); however, there was benefit in the subgroup of patients whose resuscitation was delayed more than 10 minutes from onset (Roine, 1990, 3171). The intravenous calcium channel blocker lidoflazine was compared to placebo in patients who were comatose after cardiac arrest, with no improvement in either survival or neurological outcome (LOE 1) (BRCT-2-SG, 1991, 1225). A case series of patients with coma following cardiac arrest who were treated post-arrest with thiopental suggested that, among survivors, neurological status was better than among a similar group of historical controls not treated with thiopental (LOE 3)(Monsalve, 1987, 244). However, a large randomized trial comparing thiopental loading to standard therapy in comatose survivors of cardiac arrest showed no increase in survival, no increase in survival with good neurological outcome, and no decrease in survival with poor neurological outcome with thiopental loading (LOE1) (BRCT-1-SG, 1986, 397).

Steroids had been used empirically to improve neurological outcome after cardiac arrest. However, two studies argue against this idea. A retrospective review of the database from a clinical trial of thiopental loading in comatose survivors of cardiac arrest (BRCT-1-SG, 1986, 397) was performed, in which the neurological outcomes of patients who were treated with steroids (at three different dose levels) to those who were not treated with steroids were compared (LOE 2)(Jastremski, 1989, 3427). The decision to use steroids was at the discretion of the individual clinicians. There was no difference in survival or neurological recovery in patients treated with any dose of steroids compared to those who did not receive steroids. In addition, a retrospective review of a single center experience with 459 comatose survivors of out-of-hospital cardiac arrest compared patients treated with steroids to those not so treated and found no difference in outcome (LOE 2) (Grafton, 1988, 1315).

A pseudo-randomized retrospective review compared patients who were treated with selenium to concurrent patients not treated with selenium after cardiac arrest. The decision to administer selenium was at the discretion of the treating physician based on their general belief that it might be effective, but was not based on any particular characteristic of the patients (LOE2) (Reisinger, 2009, 176). Selenium administration was associated with increased odds of regaining consciousness post arrest, after adjustment for other prognostic variables. Survival at 6 months was not associated with selenium administration.

A randomized double blind placebo controlled trial studied intravenous magnesium, intravenous diazepam, or both in 300 resuscitated patients after out-of-hospital cardiac arrest (Longstreth, 2002, 506). While there were no important adverse effects of either intervention, there was also no evidence of improved neurological outcome with either treatment or with the combination.

Finally, a single non-randomized case-series without controls found good neurological outcome in nine out of ten patients who suffered cardiac arrest during or after general anesthesia who had been treated with phenytoin (LOE 4) (Aldrete, 1981, 474). The small number of patients and uncontrolled nature of this observation preclude drawing any reliable conclusion from this study.

Acknowledgements:

Citation List
Phenytoin for brain resuscitation after cardiac arrest: an uncontrolled clinical trial.
Aldrete JA, Romo-Salas F, Mazzia VD, Tan SL.
[This was a series of 10 patients who were all treated with phenytoin after cardiac arrest, with no control group; thus the low LOE (4) and poor methodology rating. Institution: U. Alabama. COI: None reported.]


Randomized clinical study of thiopental loading in comatose survivors of cardiac arrest. Brain Resuscitation Clinical Trial I Study Group.
[No authors listed]

[This was a randomized trial but not double blinded. However the outcome was objective, so the study meets criteria for LOE 1 and good methodology ratings. Institution: U. of Pittsburgh. COI: None reported. ]


[No authors listed]

[This was a randomized double blinded placebo controlled trial, thus the LOE1, methodology "good" rating. Institution: U. of Pittsburgh. COI: None reported. ]


Steroids after cardiac arrest: a retrospective study with concurrent, nonrandomized controls.
Grafton ST, Longstreth WT Jr.
Department of Medicine, University of Washington, Seattle.

This convenience sample compared outcomes in cardiac arrest patients treated with steroids to those not so treated, thus the LOE 2/methodology "fair" rating. Institution: U. Washington. COI: None reported. ]


International Resuscitation Research Center, University of Pittsburgh, Pa.

[This was an analysis of a large clinical trial database performed to determine the effects of a treatment that was not part of the initial trial design, thus the LOE 2/methodology "fair" rating. Principal institution: SUNY Syracuse. COI: None reported.]


Randomized clinical trial of magnesium, diazepam, or both after out-of-hospital cardiac arrest. Longstreth WT Jr, Fahrenbruch CE, Olsufka M, Walsh TR, Copass MK, Cobb LA.

Department of Neurology, University of Washington, Seattle, USA. wl@u.washington.edu

[This was a randomized, double blind, placebo controlled, adequately powered trial, thus the LOE1/methodology "good" rating. Institution: U. Washington, Seattle. COI: None reported].


Intensive Care Med. 1987;13(4):244-8. Links
The neurologic effects of thiopental therapy after cardiac arrest.
Monsalve F, Rucabado L, Ruano M, Cuñat J, Lacueva V, Viñuales A.

[This was a non-randomized case series with historical controls, thus the LOE 3, Poor methodology rating. It has been superceded by reference 4. Institution: Hospital La Fe, Spain. COI: None reported].


(This study retrospectively analyzed the chance of regaining consciousness after cardiac arrest in patients treated with selenium, to those not so treated. Treatment was at the discretion of the on-duty physician (pseudo-randomization) but outcomes were objective, standardized, and assessed by a blinded examiner (LOE 2, Good methodology). Selenium was associated with increased odds or return of consciousness, but not survival. Institution: Kraneknhaus Barmherzige Schwestern, Linz, Austria. COI: none reported.)

Nimodipine after resuscitation from out-of-hospital ventricular fibrillation. A placebo-controlled, double-blind, randomized trial.
Roine RO, Kaste M, Kinnunen A, Nikki P, Sarna S, Kajaste S.

Department of Neurology, University of Helsinki, Finland.

[This was a randomized double blind placebo controlled trial (thus the LOE1 Good Quality rating) that was neutral regarding outcome. Institution: University of Helsinki. COI: None reported.]