

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 the use of neuroprotective drugs (I) as opposed to standard care (C), improve outcome (O) (e.g. 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).

resuscitation or advanced cardiac life support or cardiopulmonary resuscitation or cardio pulmonary resuscitation or reanimation or resuscitation orders or heart massage or heart arrest or cardiac arrest or circulation arrest or circulatory arrest or heart standstill or death, sudden, cardiac AND (brain hypoxia or neuronal injury or brain damage or brain ischemia or coma or unconscious or brain function) and (drug or improve* or medication or therap*) or (neuroprotec* drug* or brain protect*) AND rosc or restoration of spontaneous circulation or restore circulation or successful resuscitation or restore blood flow or restor* circulat* or success* resuscitat* or restor* flow

Result including duplicates:

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R): 79

Cochrane Central Register of Controlled Trials (2nd Quarter 2008): 20

Cochrane Database of Systematic Reviews (2nd Quarter 2008): 1

Ovid EMBASE: 87

PubMed: 95

ECC EndNote X Master library 24Mar08: 120

After removal of duplicates with Endnote (title, year, volume, issue) and manual duplicate removal: 298

• State inclusion and exclusion criteria

Inclusion criteria:

1. Cardiac arrest of all causes
2. Return of spontaneous circulation
3. Use of Neuroprotective drugs

Exclusion criteria:

1. No study of human subjects
2. Age below 18 years
3. No control group included
4. No outcome reported (survival, neurologic outcome)
5. Review article, editorial, letter or guidelines
6. Use of thrombolysis (will be evaluated in a different worksheet)

The use of magnesium after cardiac arrest is the topic of a different worksheet.

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

Due to failing inclusion criterion (1) 55 studies, due to failing inclusion criterion (2) 2 studies and due to failing inclusion criterion (3) 133 studies were not included in the analysis. Due to exclusion criterion (1) 42 studies, exclusion criterion (2) 1 study, exclusion criterion (3) 5 studies, exclusion criterion (4) 0 studies, exclusion criterion (5) 50 studies and exclusion criterion (6) 2 studies were excluded. Therefore 8 studies were included in the analysis. Of these studies 7 have been LOF 1 studies and one study LOF 2 of different neuroprotective drugs (thiopental, glucocorticoids, nimodipine, lidoflazine, diazepam, coenzyme Q10).

Summary of evidence

Evidence Supporting Clinical Question

Good	Damian, 2004, 3011 C				
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	Damian, 2004, 3011 D Roine, 1990, 3171 C,D Roine, 1993, 237 D Brain-Resuscitation-Clinical-Trial-II-Study-Group., 1991, 1225 C,D Longstreth, 2002, 506 C, D	Jastremski, 1989, 3427 C,D			
Fair	Brain-Resuscitation-Clinical-Trial-Study-Group., 1986, 397 C,D Gueugniaud, 1990, 203 C,D,E				
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 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:

It's important to emphasize that no new human studies have been published since 2004, and therefore no comparisons with the improvements made to standard CPR in C2005 are available.

One good quality LOE1 study (Damian, 2004, 3011) of a combination therapy of mild therapeutic hypothermia (35°C) and oral Coenzyme Q10 (250 mg followed by 150 mg TID for 5 days) in adult comatose patients after a witnessed cardiac arrest did show a positive effect on survival (3-month survival in the CoQ10 group was 68% (17 of 25) and 29% (7 of 24) in the placebo group (P=0.0413)). Due to the small sample size this study was underpowered to detect a difference for neurologic outcome (in the CoQ10 group, 9 of 25 patients (36%) had a good neurological outcome (GOS 4 or 5) versus only 5 of 24 (20%) in the placebo group (p=0.35; power=0.15)).

The possible side effects (dizziness or fainting, high liver enzymes, allergic reactions, nausea, vomiting, diarrhea, loss of appetite, heartburn and upper chest or throat discomfort) of Coenzyme Q10 were not addressed in the paper.

Additionally no study was available that tested the effect of Coenzyme Q10 in addition to the standard regime of therapeutic hypothermia after cardiac arrest (target temperature 32-34°C).

All other studies (Brain-Resuscitation-Clinical-Trial-II-Study-Group., 1991, 1225; Brain-Resuscitation-Clinical-Trial-Study-Group., 1986, 397; Gueugniaud, 1990, 203; Jastremski, 1989, 3427; Longstreth, 2002, 506; Roine, 1990, 3171; Roine, 1993, 237) of different neuroprotective drugs (thiopental, glucocorticoids, nimodipine, lidoflazine and diazepam) did show no difference in outcome (at least survival to hospital discharge) compared to placebo.

It seems to be reasonable to use Coenzyme Q10 as an adjunct to therapeutic hypothermia in adult comatose patients after resuscitation from witnessed cardiac arrest, although further studies are warranted to explore the effect of this drug on intact neurological survival.

Acknowledgements:

Citation List

Brain-Resuscitation-Clinical-Trial-II-Study-Group. A randomized clinical study of a calcium-entry blocker (lidoflazine) in the treatment of comatose survivors of cardiac arrest. The New England journal of medicine. 1991;324(18):1225.

Comment:

- LOE 1
- Good quality
- Neutral effect (no statistically significant difference for survival, good cerebral recovery or severe neurologic deficit within 6 months)

Brain-Resuscitation-Clinical-Trial-Study-Group. Randomized clinical study of thiopental loading in comatose survivors of cardiac arrest. N Engl J Med. 1986;314(7):397.

Comment:

- LOE 1
- Fair quality (the physicians were not blinded to treatment assignment, glucocorticoid dose was at the discretion of the treating physician (see Jastremski 1989))
- Neutral effect (no significant difference between treatment groups in survival to 1 year or good neurologic survival)

Damian MS, Ellenberg D, Gildemeister R, Lauermann J, Simonis G, Sauter W, et al. Coenzyme Q10 combined with mild hypothermia after cardiac arrest: a preliminary study. Circulation. 2004;110(19):3011.

Comment:

Combination therapy of mild therapeutic hypothermia and Coenzyme Q10

- LOE 1
- Good quality (one patient (placebo group?) did not receive study medication and was excluded)
- positive effect on survival (higher survival in CoQ10 group)
- neutral effect on neurologic outcome (no difference in neurologic outcome, in the CoQ10 group, 9 of 25 patients (36%) had a good neurological outcome (GOS 4 or 5) versus only 5 of 24 (20%) in the placebo group (p=0.35), small study (power to detect difference 0.15)

Gueugniaud PY, Gaussorgues P, Garcia-Darenes F, Bancalari G, Roux H, Robert D, et al. Early effects of nimodipine on intracranial and cerebral perfusion pressures in cerebral anoxia after out-of-hospital cardiac arrest. Resuscitation. 1990;20(3):203.

Comment:

- LOE 1
- Fair quality (there was no information on concealment of the randomisation list, the physicians were not blinded to treatment assignment)
- Neutral effect (no significant difference in terms of survival and neurologic outcome, lower intracranial pressure in nimodipine group, but similar cerebral perfusion pressure)

Jastremski M, Sutton-Tyrrell K, Vaagenes P, Abramson N, Heiselman D, Safar P, et al. Glucocorticoid treatment does not improve neurological recovery following cardiac arrest. Journal of the American Medical Association. 1989;262(24):3427.

Comment:

- LOE 2
- Good quality
- Neutral effect (none of 3 retrospectively specified glucocorticoid regimes improved survival or neurologic outcome)

Longstreth WT, Jr., Fahrenbruch CE, Olsufka M, Walsh TR, Copass MK, Cobb LA. Randomized clinical trial of magnesium, diazepam, or both after out-of-hospital cardiac arrest. Neurology. 2002;59(4):506.

Comment:

Only the diazepam vs. placebo is reported here. Magnesium evidence is the topic of a different worksheet.

- LOE 1
- Good quality (baseline imbalances, adjusted by multivariate analysis)
- Neutral effect (no difference in survival. Fewer patients awakened in the group treated with diazepam than in the placebo group within 3 months. The unadjusted difference was significant when those who received diazepam were compared with those who did not (difference -12.0%, 95% CI -22.8, -1.2%). However, the significance was lost after adjusting for baseline imbalances (difference -3.0%, 95% CI -13.5, 7.4%). The unadjusted hazard ratio for diazepam vs. placebo for time to awake was 0.64 and was significant. After adjustment for baseline imbalances using the propensity score, it was 0.97 and lost significance.)

Roine RO, Kaste M, Kinnunen A, Nikki P, Sarna S, Kajaste S. Nimodipine after resuscitation from out-of-hospital ventricular fibrillation: a placebo-controlled, double-blind, randomized trial. Jama. 1990;264(24):3171.

Comment:

Neuropsychologic data of this study are presented in Roine et al. JAMA 1993;269:237 (see below)

- LOE 1
- Good quality
- Neutral effect (no difference in 1-year survival and Glasgow Outcome Scale)

Roine RO, Kajaste S, Kaste M. Neuropsychological sequelae of cardiac arrest. J Am Med Assoc. 1993;269(2):237.

Comment:

This is the cognitive functions analysis of Roine et al. JAMA 1990;264:3171 (see above)

- LOE 1
- Good quality
- Neutral effect (nimodipine failed to show any effect on the cognitive functions tested after 3 and 12 months after cardiac arrest)