

WORKSHEET for Evidence-Based Review of Science for Veterinary CPR

1. Basic Demographics

Worksheet author(s)

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2. Clinical question:

In dogs and cats with ROSC (P), does seizure prophylaxis (I) compared to standard care (C), result in improved outcome (O) (decreased seizure, survival to discharge neurological function)?

3. Conflict of interest specific to this question:

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

4. Search strategy (including electronic databases searched):

4a. Databases

MEDLINE via PUBMED (1950 to July 2011) (performed on July 3rd 2011)

1. cardiac arrest [MeSh]
2. heart arrest [MeSh]
3. post resuscitation
4. post cardiac arrest
5. cardiopulmonary resuscitation [MeSh]
6. anticonvulsant
7. seizures

- a. 1 or 2 and 7 → 65 total hints
- b. 5 and 7 → 23 total hints
- c. 3 or 4 and 7 → 9 total hints
- d. 3 or 4 and 6 → 7 total hints

4b. Other sources

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

Inclusion criteria

Peer-reviewed articles, English language.
Interventions applied in the post-resuscitation period

Exclusion criteria

Editorials, letters, abstracts only, reviews, non-peer reviewed articles, practice guidelines, conference proceedings, book chapters, opinions, commentaries, non-English language.
Interventions applied during cardiopulmonary/cerebral resuscitation and not in the post-resuscitation period.

4d. Number of articles/sources meeting criteria for further review: 9

- Two human randomized trials were identified: (Longstreth MD et al., 2002) and (BRCT I, 1986)
- One human prospective observational study was identified: (Sunde K et al., 2007)
- Three relevant human studies were identified: (Hall RT et al., 1998), (Hui AC et al., 2005) and (Goldeberg RN et al., 1986)
- One human case report was identified: (Wijdicks EF et al., 2002)
- Two relevant animal studies were identified: (Todd MM et al., 1982) and (Ebmeyer U et al., 2000)

5. Summary of evidence**Evidence Supporting Clinical Question**

Good						<i>Hall, 1998; E=seizures incidence</i>
Fair			Ebmeyer, 2000; E=neurologic deficit			
Poor						<i>Wijdicks, 2002; E=myoclonus status epilepticus control Sunde, 2007; E=discharge rate and neurological outcome</i>
	1	2	3	4	5	6
Level of evidence (P)						

A = Return of spontaneous circulation
B = Survival of event

C = Survival to hospital discharge
D = Intact neurological survival

E = Other endpoint
Italics = Non-target species studies

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DRAFT

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

No studies directly address the clinical incidence of seizures in the post-resuscitation period in small animals. The only available data come from one experimental study in cats, in which they work on a VF induced cardiac arrest feline model (Cervantes M, 1989). This study reports a 38% incidence of electroencephalographic activity that resembles seizures after ROSC. There is no available data in the literature regarding dogs. In humans, seizures, myoclonus or both occur in 5-15% of adult patients who achieve ROSC and in up to 40% of patients who remain comatose after ROSC (Neumar RW et al., 2008). However, the true incidence of post-resuscitation seizures could be larger since the incidence of electrographic seizures may be higher as their clinical diagnosis may not always be accurate. It is well established that prolonged and untreated seizures can cause cerebral injury in a number of ways (increase of cerebral metabolism by up to 3-fold and neuronal necrosis in different cerebral regions). On the other hand, seizures in the post-resuscitation period have been associated with episodes of ictal bradycardia/asystole (Wolber T, 2010) and ictal hypoventilation/apnea that could be involved in the pathogenesis of Sudden Unexpected Death in Epilepsy (SUDEP) (Lathoo SD, 2010).

As for specific projects that study the effects of anticonvulsant therapy after cardiac arrest in humans, two randomized controlled studies in adults can be found in the literature. The first one, the Brain Resuscitation Clinical Trial I (BRCT I) in 1986 (BRCT I, 1986) studied the effect of Thiopental administered after ROSC to randomly assigned comatose survivors of cardiac arrest. Although it reduced seizure activity, intracranial pressure, edema formation, brain metabolism and diminished the damage by focal and incomplete ischemia, it failed to prove a significantly better neurological outcome at the end of one year of follow up. The second study was carried out by Longstreth et al. (Longstreth WT et al., 2002). It combined the administration of magnesium and diazepam, and it also reported neurological outcomes that were not different from treatment with placebo. However, a prospective observational study by Sunde et al. (Sunde K et al., 2007) proved that the implementation of a standardized treatment protocol for post resuscitation care after cardiac arrest, that included prophylaxis and treatment of seizures, contributed to better overall and neurological outcome. In any case, there is indication in the literature (Hui AC et al., 2005) that the control of seizures in post cardiac arrest patients is difficult, since multiple drugs are needed to achieve an effective control.

There are two randomized controlled trials in neonates with severe perinatal asphyxia that present conflicting results. In Hall et al (Hall et al., 1998) treatment with phenobarbital compared with the control group was associated with a 27% reduction in the incidence of seizures and a significant improvement in neurologic outcome at 3 years of age. While, Goldberg et al. (Goldberg et al., 1986) found that the administration of thiopental was associated with similar degree of seizure activity, increased incidence of hypotension and greater requirements of blood pressure support compared to the control group. In addition, no differences were found between the two groups as far as neurologic, cognitive and motor outcome are concerned. Apart from studies with barbiturates, one case report (Wijdicks EFM et al., 2002) indicated that Propofol helped achieve an optimal control of myoclonus status epilepticus in comatose patients following cardiac arrest. However, the small number of individuals reported here grants very limited evidence to this case report.

In small animals we can only refer to two experimental trials of thiopental alone or thiopental combined with phenytoin and methylprednisolone, one being carried out in cats and another one in dogs. Thiopental combined with phenytoin and methylprednisolone was proven to increase the neuroprotective effect of hypothermia in dogs (Ubmeyer U et al., 2000), whereas the beneficial effects of the administration of thiopental alone seemed to be offset by a number of cardiovascular and respiratory side effects. Thiopental administration to cats after ROSC showed mixed results (Todd MM et al., 1982). On one hand it proved to increase survival rates by suppressing unusual post-arrest EEG patterns but showed no effect on the neurologic function of survivors.

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: In conclusion, more clinical data are needed to define the effects of prophylactic anticonvulsant therapy after ROSC in the post-arrest period on both humans and small animals. For the time being, the

available literature is very limited and very heterogeneous in nature. Although a number of studies on thiopental loading in brain ischemia animal models had shown promising results (Bleyaert AL et al., 1978; Nemoto EM et al., 1977; Smith AL et al., 1974; Michenfelder JD et al., 1976 and Yatsu FM et al., 1972), experimental and randomized controlled trials in post-arrest patients of different species have shown mixed results. One LOE 3 study (Ebmeyer U et al., 2000) shows beneficial effects in dogs, although systemic side effects are also reported depending on the dose. Two LOE 6 studies in humans (BRCT I, 1986; Longstreth WT et al., 2002) show no difference between treatment and control groups. One LOE 3 study in cats (Todd MM et al., 1982) proves mixed results in final outcome. The use of benzodiazepines remains the first line treatment for seizures in the post arrest scenario, although an effective control of seizures in these patients seems to be more difficult to achieve (Hui AC et al., 2005). Another treatment option seems to be Propofol, however the available literature is not solid enough to support this hypothesis (Wijdicks et al., 2002). Despite the lack of solid evidence for the prophylactic use of anticonvulsant therapy in the post resuscitation period, one prospective observational trial LOE 6 (Sunde K et al., 2007) showed improved neurological and overall outcomes when effective and proactive treatment of seizures was established as part of a standardized post resuscitation care treatment protocol. A protocol in which proactive control of seizures was highly encouraged, however other measures were also taken as part of the protocol, therefore adding to the confounding factors in the final outcome.

8. Acknowledgement

9. Citation list

BRCT I (1986). "Randomized clinical study of thiopental loading in comatose survivors of cardiac arrest. Brain Resuscitation Clinical Trial I Study Group." (N Engl J Med 1986; 314: 397-403)

After restoration of spontaneous circulation and adequate oxygenation, 262 comatose survivors of cardiac arrest were randomly assigned to receive standard brain-oriented intensive care or the same standard therapy plus a single intravenous loading dose of thiopental (30 mg per kilogram of body weight). The study was designed to have an 80 percent probability of detecting a 20 percent reduction in the incidence of permanent postischemic cerebral dysfunction. Base-line characteristics were similar in the two treatment groups. At the end of one year of follow-up, there was no statistically significant difference between treatment groups in the proportion of patients who died (77 percent of the thiopental vs. 80 percent of the standard-therapy group), survived with "good" cerebral recovery (20 percent of the thiopental vs. 15 percent of the standard-therapy group), or survived with permanent severe neurologic damage (2 percent of the thiopental vs. 5 percent of the standard-therapy group). The results of this study do not support the use of thiopental for brain resuscitation after cardiac arrest.

Level 6, Neutral, funding: NIH Grant (NS 15295-01-4).

Key Points:

Ebmeyer U, Safar P et al. (2000) "Thiopental combination treatments for cerebral resuscitation after prolonged cardiac arrest in dogs. Exploratory outcome study." Resuscitation. 2000 Jul;45(2):119-31

We postulate that mitigating the multifactorial pathogenesis of postischemic encephalopathy requires multifaceted treatments. In preparation for expensive definitive studies, we are reporting here the results of small exploratory series, compared with historic controls with the same model. We hypothesized that the brain damage mitigating effect of mild hypothermia after cardiac arrest can be enhanced with thiopental loading, and even more so with the further addition of phenytoin and methylprednisolone. Twenty-four dogs (four groups of six dogs each) received VF 12.5 min no-flow, reversed with brief cardiopulmonary bypass (CPB), controlled ventilation to 20 h, and intensive care to 96 h. Group 1 with normothermia throughout and randomized group 2 with mild hypothermia (from reperfusion to 2 h) were controls. Then, group 3 received in addition, thiopental 90 mg/kg i.v. over the first 6 h. Then, group 4 received, in addition to group 2 treatment, thiopental 30 mg/kg i.v. over the first 90 min (because the larger dose had produced cardiopulmonary complications), plus phenytoin 15 mg/kg i.v. at 15 min after reperfusion, and methylprednisolone 130 mg/kg i.v. over 20 h. All dogs survived. Best overall performance categories (OPC) achieved (OPC 1 = normal, OPC 5 = brain death) were better in group 2 than group 1 ($P < 0.05$) and numerically better in groups 3 or 4 than in groups 1 or 2. Good cerebral outcome (OPC 1 or 2) was achieved by all six dogs only in group 4 ($P < 0.05$ group 4 vs. 2). Best NDS were 44 +/- 3% in group 1; 20 +/- 14% in group 2 ($P = 0.002$); 21 +/- 15% in group 3 (NS vs. group 2); and 7 +/- 8% in group 4 ($P = 0.08$ vs. group 2). Total brain histologic damage scores (HDS) at 96 h were 156 +/- 38 in group 1; 81 +/- 12 in group 2 ($P < 0.001$

vs. group 1); 53 +/- 25 in group 3 (P = 0.02 vs. group 2); and 48 +/- 5 in group 4 (P = 0.02 vs. group 2). We conclude that after prolonged cardiac arrest, the already established brain damage mitigating effect of mild immediate postarrest hypothermia might be enhanced by thiopental, and perhaps then further enhanced by adding phenytoin and methylprednisolone.

Level 3, Supporting, funding: A.S. Laerdal Foundation and US Navy Medical research and Development Command.

Goldberg RN, Moscoso P et al. (1986) "Use of barbiturate therapy in severe perinatal asphyxia: a randomized controlled trial." J Pediatr. 1986 Nov;109(5):851-6.

The possible cerebral sparing effect of thiopental was evaluated in 32 severely asphyxiated neonates randomly assigned to either a thiopental treatment or control group. All infants had neurologic manifestations of asphyxia and required assisted ventilation. Thiopental was begun at a mean age of 2.3 hours and was given as a constant infusion that delivered 30 mg/kg over 2 hours. Treatment was continued at a lower dose for 24 hours. Seizure activity occurred in 76% of infants given thiopental and 73% of control infants at a mean age of 1.5 and 2.5 hours, respectively. Although initial arterial blood pressure was similar in both groups, hypotension occurred in 88% of treated and 60% of control infants. The amount of blood pressure support required was significantly greater (P less than 0.005) in the thiopental treatment group. Three infants died in the control group, and five in the treatment group. Developmental assessment was performed at a minimum of 12 months of age in 22 infants. There were no significant differences in neurologic, cognitive, or motor outcome between groups. Deteriorating performance over time was a consistent trend in both groups. These findings indicate that treatment of severe perinatal asphyxia with thiopental does not appear to have a cerebral sparing effect and may be associated with significant arterial hypotension.

Level 6, Opposing, funding:

Key Points:

Hall RT, Hall FK, Daily DK (1998). "High-dose phenobarbital therapy in term newborn infants with severe perinatal asphyxia: a randomized, prospective study with three-year follow-up." J Pediatr. 1998 Feb;132(2):345-8.

OBJECTIVE: To determine whether 40 mg/kg phenobarbital given to term infants with severe asphyxia would result in a lower incidence of seizures in the newborn period and an improved neurologic outcome. **METHODS:** We conducted a randomized, controlled, prospective study. Entry criteria included (1) an initial arterial pH less than or equal to 7.0 with a base deficit 15 mEq/L or more, (2) Apgar score less than or equal to 3 at 5 minutes of age, or (3) failure to initiate spontaneous respiration by 10 minutes of age. Sample size was calculated to detect a 50% reduction in the incidence of neonatal seizures. **RESULTS:** No differences were present between treatment and control groups with respect to severity of asphyxia assessed by initial arterial pH, base excess, cerebrospinal fluid lactate dehydrogenase concentration or detection of CSF creatine kinase of its BB isoenzyme. Seizures occurred in 9 of 15 infants in the treatment group and 14 of 16 infants in the control group (p = 0.11). No adverse effects were observed from phenobarbital on heart rate, respiratory rate, blood pressure, or arterial blood gas values. Three-year follow-up revealed normal outcome in 11 of 15 infants in the treatment group and 3 of 16 in the control group (p = 0.003). **CONCLUSION:** Phenobarbital, when administered in a dose of 40 mg/kg intravenously over 1 hour in term, severely asphyxiated newborn infants appeared to be safe and was associated with a 27% reduction in the incidence of seizures and a significant improvement in neurologic outcome at 3 years of age.

Level 6, Supporting, funding:

Key Points:

Hui AC, Cheng C, Lam A, Mok V, Joynt GM. Prognosis following Postanoxic Myoclonus Status epilepticus. Eur Neurol. 2005;54(1):10-3.

Prediction of outcome after cardiac arrest has important ethical and socioeconomic implications. In general, delay in recovery of neurological function is associated with a worse prognosis. The presence of myoclonic seizures early after anoxia has been identified as a poor prognostic factor. We report a series of patients who developed postanoxic myoclonus status epilepticus (MSE), which was defined as continuous myoclonic seizure activity lasting 30 min or more. The results from 18 patients were retrieved, 11 men and 7 women, age ranging from 29 to 90 years. Myoclonus developed a mean of 11.7 h after cardiac arrest, persisting for a mean of 60.5 h. Sixteen (89%) died following MSE and the 2 survivors were highly dependent or remained in a persistent vegetative state, supporting the view that prognosis is poor in this condition.

Level 6, Neutral, funding: SK Yee Medical Foundation (project No.200126).

Key points: indication of the difficulty in controlling these seizures was that multiple antiepileptic drugs were required during hospitalization, in fact, apart from intermittent benzodiazepine therapy a total of 42 antiepileptic drugs were given to these 18 cases (average of 2.3 drugs per patient). Limitations: limited number

Longstreth WT Jr, Fahrenbruch CE et al. (2002) "Randomized clinical trial of magnesium, diazepam, or both after out-of-hospital cardiac arrest." Neurology. 2002 Aug 27;59(4):506-14.

OBJECTIVE: To evaluate the feasibility, safety, and efficacy of interventions aimed at improving neurologic outcome after cardiac arrest. **METHODS:** The authors conducted a double-blind, placebo-controlled, randomized clinical trial with factorial design to see if magnesium, diazepam, or both, when given immediately following resuscitation from out-of-hospital cardiac arrest, would increase the proportion of patients awakening, defined as following commands or having comprehensible speech. If the patient regained a systolic blood pressure of at least 90 mm Hg and had not awakened, paramedics injected IV two syringes stored in a sealed kit. The first always contained either 2 g magnesium sulfate (M) or placebo (P); the second contained either 10 mg diazepam (D) or P. Awakening at any time by 3 months was determined by record review, and independence at 3 months was determined by telephone calls. Over 30 months, 300 patients were randomized in balanced blocks of 4, 75 each to MD, MP, PD, or PP. The study was conducted under waiver of consent. **RESULTS:** Despite the design, the four treatment groups differed on baseline variables collected before randomization. Percent awake by 3 months for each group were: MD, 29.3%; MP, 46.7%; PD, 30.7%; PP, 37.3%. Percent independent at 3 months were: MD, 17.3%; MP, 34.7%; PD, 17.3%; PP, 25.3%. Significant interactions were lacking. After adjusting for baseline imbalances, none of these differences was significant, and no adverse effects were identified. **CONCLUSIONS:** Neither magnesium nor diazepam significantly improved neurologic outcome from cardiac arrest.

Level 6, Neutral, funding: supported by a gift from the Medic One Foundation.

Key Points:

Sunde K, Pytte M et al. (2007). "Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest." Resuscitation. 2007 Apr;73(1):29-39.

BACKGROUND: Mortality among patients admitted to hospital after out-of-hospital cardiac arrest (OHCA) is high. Based on recent scientific evidence with a main goal of improving survival, we introduced and implemented a standardised post resuscitation protocol focusing on vital organ function including therapeutic hypothermia, percutaneous coronary intervention (PCI), control of haemodynamics, blood glucose, ventilation and seizures. **METHODS:** All patients with OHCA of cardiac aetiology admitted to the ICU from September 2003 to May 2005 (intervention period) were included in a prospective, observational study and compared to controls from February 1996 to February 1998. **RESULTS:** In the control period 15/58 (26%) survived to hospital discharge with a favourable neurological outcome versus 34 of 61 (56%) in the intervention period (OR 3.61, CI 1.66-7.84, $p=0.001$). All survivors with a favourable neurological outcome in both groups were still alive 1 year after discharge. Two patients from the control period were revascularised with thrombolytics versus 30 (49%) receiving PCI treatment in the intervention period (47 patients (77%) underwent cardiac angiography). Therapeutic hypothermia was not used in the control period, but 40 of 52 (77%) comatose patients received this treatment in the intervention period. **CONCLUSIONS:** Discharge rate from hospital, neurological outcome and 1-year survival improved after standardisation of post resuscitation care. Based on a multivariate logistic analysis, hospital treatment in the intervention period was the most important independent predictor of survival.

Level 6, Supporting, funding: Laerdal Foundation for Acute Medicine, Ulleval University Hospital Scientific Advisory Council and Health Region East.

Key points: the standardized treatment protocol for post-resuscitation care implemented includes "prevention/treatment of seizures" by "increase sedation, or specific anticonvulsive medication, EEG when indicated (early contact with a neurologist).

Todd MM, Chadwick HS et al. (1982) "The neurologic effects of thiopental therapy following experimental cardiac arrest in cats." Anesthesiology. 1982 Aug;57(2):76-86.

To define the utility of high-dose barbiturate therapy following an episode of complete global cerebral ischemia, we investigate the effects of 60 mg/kg of thiopental given to cats five minutes after resuscitation from 12, 14, or 16 min of electrically induced ventricular fibrillation (VF). All aspects of the arrest, resuscitation, with post-arrest care were carefully controlled, with the EEG becoming isoelectric 20-25 s after the onset mean resuscitation time of 2.5 +/- 0.2 (SEM) min. For any given duration of VF, there were no differences (control vs thiopental) in any pre- or post-arrest parameters (blood pressure, blood gases, electrolytes, etc.) A total of 68 resuscitated cats were entered into various treatment and

control groups, and all but one group received 20-24 h of post-resuscitation paralysis, mechanical ventilation, and ICU support before being extubated. Cats received an additional six days of aggressive nursing care, and daily examinations were performed with the assignment of a neurologic deficit score (NDS) between 0 (normal) and (brain dead). Autopsies were performed to determine the cause of death in animals which died before the end of the seven-day observation period. The early post-arrest period was marked by the occurrence of repetitive, rhythmic bursts of high-frequency electroencephalographic (EEG) activity (? seizures) in 38 per cent of control animals (16/42, all arrest times combined). Ten of these animals died as a result of severe neurologic injuries. By contrast, only 12 per cent of treated cats (3/26) developed similar EEG patterns (P less than 0.05) and there were no neurologic deaths in the thiopental groups. The differences in the incidence of neurologic deaths (control vs. thiopental) was significant (P less than 0.02). The change in overall mortality did not quite reach significance (36 per cent vs. 21 per cent), and treatment had no effect on the incidence of deaths due to cardiovascular causes (e.g., myocardial infarctions). In spite of the effects on mortality, treatment had no effect on the neurologic function of survivors (assessed by NDS). These findings suggest that thiopental improved survival rates by suppressing an unusual post-arrest EEG pattern (? anticonvulsant effect), but had no additional cerebral protective effects.

Level 3, Neutral, funding: Veteran's Administration, NIH Grant (NS-13679-02) and Bank of America-Giannini Foundation.
Key Points:

Wijdicks EF (2002). "Propofol in myoclonus status epilepticus in comatose patients following cardiac resuscitation". J Neurol Neurosurg Psychiatry. 2002 Jul;73(1):94-5.

Myoclonus status epilepticus has been identified as a poor prognosticating sign in comatose patients following cardiopulmonary resuscitation. These vigorous generalised jerks are considered to be the penultimate phenomenon in a severely damaged brain that is difficult to manage and that may cause difficulty in ventilating the patient. Antiepileptic drugs such as phenytoin or benzodiazepines have not been very successful. When the jerks are particularly severe, neuromuscular junction blockers have been recommended. I report on two comatose patients with myoclonus status epilepticus. Propofol in a subanaesthetic dose muted these movements considerably. Propofol has not been used in this condition before but has been effective in two earlier case reports of severe myoclonus: one patient had chloralose poisoning and one had "encephalopathy." In this condition a catastrophic anoxic-ischaemic injury may have damaged the cortex, basal ganglia, brain stem, and spinal cord and thus the origin of myoclonus remains undetermined. Propofol may terminate myoclonus through enhancement of γ amino butyric acid type A receptor. Further experience is needed, but these case reports indicate that good control can be achieved. Propofol's additional benefit is that intermittent neurological assessment remains reliable after discontinuation of propofol.

Level 6, Supporting, funding: none.

Key Points: