

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 after cardiac arrest (P), does the administration of mannitol / hypertonic saline (I) compared to standard care (C), result in improved outcome (O) (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 (performed on April 20, 2011)

1. ROSC AND brain injury – 34 hits
2. #1 AND mannitol or hypertonic saline AND survival to discharge – 15 hits
3. Resuscitation or CPR AND Mannitol or hypertonic saline AND veterinary patients – 4 hits
4. Mannitol or hypertonic saline AND cardiac arrest - 248 hits
5. ROSC AND mannitol – 1 hits
6. ROSC AND hypertonic saline – 7 hits

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- Resuscitation or CPR or ROSC AND Mannitol – 12 hits
 Resuscitation or CPR or ROSC AND hypertonic saline – 1 hit
 Hypoxic brain injury AND Mannitol - 0 hits
 Hypoxic brain injury AND hypertonic saline – 0 hits

4b. Other sources

-In addition all references of identified articles already in review

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

Inclusion criteria

Use of mannitol or hypertonic saline for resuscitation in patients with cardiac arrest

Exclusion criteria

Abstracts only. Editorials, Articles in language other than English

4d. Number of articles/sources meeting criteria for further review: 8

- 2 veterinary retrospective – Hofmeister 2009, Kass 1992
- 4 randomized controlled studies using porcine model of cardiac arrest – Fischer 2002, Breil 2003, Krep 2004, Krieter 2002
- 1 randomized pre-clinical human pilot study – Bender 2007

- 1 randomized controlled human trial – Larson 2002

5. Summary of evidence

Evidence Supporting Clinical Question

Good						
Fair				Hofmeister 2009; C		
Poor						<i>Bender 2007; B – Short term survival Fischer 2002; E= Myocardial perfusion pressure E= Myocardial blood flow Breil 2002; E = myocardial perfusion pressure E=myocardial blood flow Krep 2004; E=Cerebral blood flow Krieter 2002; E=myocardial & cerebral damage</i>
	1	2	3	4	5	6
Level of evidence (P)						

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Deleted: Fischer 2002; E= Myocardial perfusion pressure E= Myocardial blood flow - Bender 2007; B – Short term survival survival

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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

Evidence Neutral to Clinical question

Good						
Fair						
Poor				Kass 1992; B		<i>Larsen 2002; E=Malondialdehyde</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

Evidence Opposing Clinical Question

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

Both mannitol and hypertonic saline are used in the resuscitation of veterinary patients. The use of these hyperoncotic fluids appears to be based primarily on mechanistic reasoning, clinician preference and the underlying cause of arrest. There is very minimal solid evidence in the literature of the use of mannitol in patients during CPR. There is one human clinical trial evaluating its use in patients undergoing cardiopulmonary bypass procedures, this study measures malondialdehyde as a reflection of myocardial ischemia/reperfusion injury (LOE [6](#)) (Larsen 2002). This is a small clinical study (33 subjects) in a population of patients undergoing elective, first time myocardial revascularization procedure. This study is difficult to draw conclusions regarding the use of mannitol in CPR because the dose of mannitol is much higher than the average clinical dose (4-8 g/l mixed with cardioplegia) and it is delivered directly via an aortic root cannula. The study was attempting to evaluate the oxygen free radical scavenging capability of Mannitol during aortic cross clamping. This study failed to show any reduction of free radical activity during aortic cross clamping in the patients administered either dose of Mannitol mixed with the cardioplegia. (Larsen 2002) There is one veterinary retrospective (Kass 1992) that mentions mannitol use in CPR, however this intervention is grouped with other interventions and there is no specific data to support or refute the use of mannitol in this paper. Finally, there is mention of indirect association with improved survival in patients given [mannitol](#) among other interventions. (Hofmeister, 2009) This is a retrospective work and the use of this intervention was not specifically evaluated separately from other interventions. The evidence evaluating use of hypertonic saline in CPR is much stronger, much of the work is done using porcine models of cardiopulmonary arrest as well as a few clinical trials with human subjects. There is mounting evidence suggesting that hypertonic saline improves myocardial blood flow, myocardial perfusion pressure, (LOE [6](#)) (Fischer 2002, Breil 2002) and cerebral blood flow (LOE [6](#)) (Krep 2004) and decreases myocardial and cerebral damage (Krieter 2002). Breil, et.al did not report an enhanced effect when combining hypertonic saline with hydroxyethyl starch. There is one small (66 patients) pre-clinical pilot study in humans that suggests that hypertonic saline/hydroxyethyl starch may improve short term survival (LOE [6](#)) (Bender 2007), they did not assess hypertonic saline as a sole agent. Patients included suffered out of hospital arrests and were given the HHS prior to hospital admission. Though the paper was not powered enough to identify statistically significant benefit, the patients receiving HHS showed a trend toward higher success of resuscitation and a higher rate of admission to the hospital.

There is insufficient evidence to provide recommendation for or against the use of mannitol in CPR. Randomized controlled trials are needed to evaluate the effects of this intervention. Based on existing evidence there may be benefit to use of hypertonic saline with or without hydroxyethyl starch for improvement of myocardial and cerebral blood flow and reduction of ischemia/reperfusion injury, [when given during CPR](#). However, there is no data available evaluating its use and effect when administered during the post-resuscitation phase.

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: Scant information was identified on the use of mannitol in direct clinical trials. There is indirect evidence in retrospective studies suggesting a positive effect using mannitol in CPR (LOE 4) (Hofmeister 2009). There is one human clinical trial evaluating its use in patients undergoing cardiopulmonary bypass procedures, this study measures malondialdehyde as a reflection of myocardial ischemia/reperfusion injury (LOE [6](#)) (Larsen 2002). There is one veterinary retrospective (Kass 1992) that

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Comment [1]: Seems that these are all intraarrest papers though. There is nothing for post-arrest?

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does not assess mannitol specifically. The evidence evaluating use of hypertonic saline in CPR is much stronger (Bender 2007; Breil 2002; Fischer 2002; Krep 2004; Krieter 2002), much of the work is done in swine and humans. There is a fair amount of evidence suggesting the hypertonic saline improves myocardial blood flow, myocardial perfusion pressure, (LOE 6) (Fischer 2002, Breil 2002) and cerebral blood flow (LOE 6) (Krep 2004) and decreases myocardial and cerebral damage (Krieter 2002). There is one small pre-clinical pilot study in humans that suggests that hypertonic saline/hydroxyethyl starch may improve short term survival (LOE 6) (Bender 2007). Based on existing evidence no recommendation for or against the use of mannitol after ROSC can be made. Based on existing evidence there may be benefit to intra-arrest use of hypertonic saline with or without hydroxyethyl starch for improvement of myocardial and cerebral blood flow and reduction of ischemia/reperfusion injury. However, more data is required to recommend routine intra-arrest use. No specific recommendation can be made for its post-resuscitation use.

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8. Acknowledgement

9. Citation list

Hofmeister, E.H., Brainard, B.M., et al.. (2009). "Prognostic indicators for dogs and cats with cardiopulmonary arrest treated by cardiopulmonary cerebral resuscitation at a university teaching hospital." JAVMA 235(1): 51-7.

SUMMARY: Retrospective study using medical record search to identify variables associated with prognosis for ROSC in veterinary patients.

Level 4, supporting, funding: none sought or received

Key points: Cross-sectional animal retrospective, Mannitol is indirectly identified as associated with ROSC among several other therapies.

Breil, M., Krep, H., Sinn, D., Hagendorff, A., Dahmen, A., Eichelkraut, W., Hoefft, A., Fischer, M. (2003). "Hypertonic saline improves myocardial blood flow during CPR, but is not enhanced further by the addition of hydroxy ethyl starch." Resuscitation 56(3): 307-317.

SUMMARY: Small randomized trial using porcine model of cardiac arrest, 32 domestic swine, open chest CPR initiated after 8 minutes of ventricular fibrillation. Animals randomly received 2 ml/kg per 10 minutes of hypertonic saline, hypertonic saline/hydroxyethyl starch, hydroxyethylstarch or normal saline. Hemodynamic values monitored continuously. Hypertonic saline and hypertonic saline/HES significantly increased myocardial blood flow, resuscitation success and 240 minute survival rate.

Level 2, supporting, Funding: none listed

Key points: Small randomized controlled trial using porcine model of cardiac arrest. Endpoints include MPP, MBF and CI.

Kass, P., Haskins, S. (1992). "Survival following cardiopulmonary resuscitation in dogs and cats" JVECC 2(2): 57-65.

SUMMARY: Retrospective, uncontrolled study evaluating medical records for cause of cardiac arrest and for survival following CPR.

Level 4, neutral, Funding: none listed

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Key points: retrospective, mannitol was grouped with other interventions.

Krep, H., Breil, M., Sinn, D., Hagendorff, A., Hoeft, A., Fischer, M. (2004) "Effects of hypertonic versus isotonic infusion therapy on regional cerebral blood flow after experimental cardiac arrest in cardiopulmonary resuscitation in pigs" *Resuscitation* 63 (1): 73-83

SUMMARY: Small randomized controlled trial evaluating the effects of hypertonic, isooncotic and isotonic fluids on cerebral blood flow during and after CPR. 32 domestic swine were used with open chest CPR after 8 minutes of ventricular fibrillation. Animals were randomly assigned to receive 2 ml/kg per 10 minutes of hypertonic saline, hypertonic-isooncotic HES/saline, isooncotic HES or isotonic saline. CBF measured using colored microspheres before cardiac arrest, during CPR and at 20, 90 and 240 minutes after ROSC. In HES/NaCl group CBF decreased significantly. In HS/HHS treated group CBF was sustained during and after CPR and was significantly higher than animals receiving normal saline. Animals receiving HES and NS showed evidence of severe post-ischemic hypoperfusion as indicated by a decrease of CBF below the pre-arrest level.

Level 2: supporting; Funding: none listed

Key Points: small randomized controlled trial, non-target species

Krieter, H. Denz, C. Janke, C. Bertsch, T. Luiz, T. Ellinger K, van Ackern, K. (2002) "Hypertonic-hyperoncotic solutions reduce the release of cardiac troponin I and S-100 after successful cardiopulmonary resuscitation in pigs" *Anesthesia & Analgesia* 95(4): 1031-1036.

SUMMARY: Sixteen domestic swine were randomized and used to investigate the effect of infusion of either normal saline, or a hypertonic saline/HES mixture after cardiac arrest. Advanced cardiac life support was initiated after 4 minutes of non-intervention and 1 minute of basic life support. HHS and NS were administered after ROSC. Serum cardiac troponin I and S-100 were measured up to 240 minutes after ROSC. Troponin and S-100 increased in all animals, however the increase was significantly blunted in animals that received HHS compared to those receiving placebo.

Level 2: supporting; Funding – none listed

Key points: Small randomized trial, non-target species

Larsen M., Webb G., Kennington S., Kelleher N., Sheppard J., Kuo J., Unsworth-White J. (2002) "Mannitol in cardioplegia as an oxygen free radical scavenger measured by malondialdehyde." *Perfusion* 17(1): 51-55.

SUMMARY: Human trial evaluating the free radical scavenging ability of Mannitol. Mannitol (4-8 ml/l) was added to the cardioplegia and administered antegrade into the aortic root. Study measures malondialdehyde using HPLC. Malondialdehyde is an endproduct of lipid peroxidation that causes cellular damage and disruption of cell membranes and thus is an indicator of anti-oxidant exhaustion secondary to oxygen free radical production. No statistical difference was identified among the three groups (4ml/l, 8 ml/l and no mannitol).

Level 5: opposing; Funding: none listed

Key points: small randomized trial, non-target species, study endpoints are not endpoints for CPR, however the study speaks to mechanistic reasoning for use of this drug as a free radical scavenger in those suffering ischemia reperfusion injury.

Bender R., Breil M., Heister U., Dahmen A., Hoeft A., Krep H., Fischer M. (2007) "Hypertonic saline during CPR: Feasibility and safety of a new protocol of fluid management during resuscitation" *Resuscitation* 72(1) 74-81.

SUMMARY: Randomized controlled pre-clinical trial evaluating human patients during out of hospital arrest. Subjects randomly assigned to receive 2 ml/kg/10 minutes of hypertonic saline/6% HES or HES alone. Hemoglobin, blood gases, sodium/potassium were measured before and 10 minutes after infusion and after admission to the hospital. Sixty six patients were included in the trial. Patients receiving hypertonic saline/HES mixture showed a trend toward higher ROSC and hospital admission. This effect was more pronounced in patients with a duration of untreated cardiac arrest greater than 6 minutes or if the arrest rhythm was either asystole or pulseless electrical activity.

Level 3: supporting: Funding: none listed

Key Points: small pre-clinical trial, non-target species. Trend toward increased ROSC particularly in patients with asystole or PEA as the arrest rhythm.

Fischer M., Dahmen A., Standop J., Hagendorff A., Hoefl A., Krep H. (2002) "Effects of hypertonic saline on myocardial blood flow in a porcine model of prolonged cardiac arrest." *Resuscitation* 54(3): 269-280.

SUMMARY: Randomized controlled trial using 21 domestic swine. Open chest cardiac massage was initiated 10 minutes after ventricular fibrillation. Animals were randomized to receive hypertonic saline (4 ml/kg/20 min) or normal saline (2 mls/kg/10 min). Continuous hemodynamic monitoring performed during and after CPR/ROSC. Colored microspheres were used to measure myocardial blood flow and cardiac index before cardiac arrest, during CPR and 5, 30 and 120 minutes after ROSC. During CPR hypertonic saline significantly increased myocardial perfusion pressure, myocardial blood flow and cardiac index in comparison to saline. Hypertonic saline also significantly increased survival rate at 120 minutes.

Level 2: supporting: Funding: none listed

Key points: Small randomized, controlled clinical trial, non-target species