WORKSHEET for Evidence-Based Review of Science for Veterinary CPCR

1. Basic Demographics

Worksheet author(s)

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2. Clinical question:

In dogs and cats with cardiac arrest (asystole, pulseless electrical activity, pulseless VT and VF) (P), does the use of calcium alone or combination with other drugs (I) compared to not using calcium (C), improve outcomes (e.g ROSC, survival) (O)

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

Keywords
1. Calcium
2. Cardiopulmonary arrest
3. Cardiopulmonary resuscitation
4. Ventricular fibrillation
5. Pulseless electrical activity
6. Canine
7. Feline

Search Most Recent Queries Time Result
#27 Search calcium and ventricular fibrillation 16:44:19 1280
#3 Search calcium AND cardiopulmonary resuscitation 16:41:44 210
#2 Search calcium AND cardiopulmonary arrest 16:23:28 1700
#9 Search calcium AND cardiopulmonary arrest AND feline 14:57:50 11
#8 Search calcium AND cardiopulmonary arrest AND canine 12:45:28 223
#5 Search calcium AND pulseless electrical activity 12:43:41 7

CAB
Calcium AND cardiopulmonary arrest: 0
Calcium AND ventricular fibrillation: 13
Calcium AND cardiopulmonary resuscitation: 2
Calcium AND cardiopulmonary arrest AND Feline: 0
Calcium AND cardiopulmonary arrest AND canine: 0
Calcium AND pulseless electrical activity: 0

4b. Other sources

-GOOGLE SCHOLAR
Calcuim and Cardiopulmonary resuscitation: 37,000. Did not go through all references due to vast amount.

Calcium AND cardiopulmonary arrest: 17,600. Did not go through all references due to vast amount)
Calcium AND ventricular fibrillation: 63,200 Did not go through all references due to vast amount
Calcium AND cardiopulmonary arrest AND Feline: 3100
Calcium AND cardiopulmonary arrest AND canine: 17,000 Did not go through all references due to vast amoun)
Calcium AND pulseless electrical activity: 2810

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

Inclusion criteria

Use of calcium in human patients, dogs and cats undergoing cardiopulmonary arrest. Only peer reviewed literature reviewed

Exclusion criteria

The following studies were excluded: Non true cardiac arrest models, editorials, review articles, use of calcium products not associated with cardiac arrest, use of calcium channel blockers during cardiac arrest, use of calcium sensitizing agents during cardiac arrest.

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

There were 9 papers meeting the criteria for further review

5. Summary of evidence

Evidence Supporting 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

Evidence Neutral to Clinical question

Good						*Stueven, 1985*[A, C]
Fair						
Poor						*Harrison 1983*[A, B, C] *Gando 1988* [A]
	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						*Stueven, 1984;*[A, C] *Stueven 1985,*[A,B,C] *Walraven, 1998* [A, B, D]
Fair	*Blecic 1987* [A, B]		*Meuret, GH 1984* [A]			
Poor						*Stueven, 1983*[A, C]
	1	**2**	**3**	**4**	**5**	**6**
Level of evidence (P)						

A = Return of spontaneous circulation
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D = Intact neurological survival
E = Other endpoint
Italics = Non-target species studies

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

The use of calcium during cardiopulmonary and cerebral resuscitation (CPCR) is thought to enhance myocardial contractility and ventricular automaticity during asystole. Its use however has remained controversial and there has not been a single study that overwhelmingly demonstrates the beneficial effects of calcium in patients with cardiopulmonary arrest (CPA). Subsequently there are very few studies evaluating the use of calcium in CPCR. Most studies evaluated were performed in the 80's and they all either discount the use of calcium or have very weak evidence to support its use during CPCR. There were few animal studies investigating the use of calcium in CPA and none of these were clinical studies.

Studies have demonstrated ionized hypocalcemia in human patients that suffered CPA (Urban 1988). Cairns (1991) was also able to document that ionized hypocalcemia occurs during prolonged cardiac arrest in dogs. However, it has been difficult to document that supplemental calcium administration improves the efficacy of CPCR.

Harrison in 1983 retrospectively evaluated records of cardiac arrest patients presenting to an EMS system. In this review, only patients with electromechanical dissociation (Pulseless electrical activity PEA) appeared to respond to the calcium injection (given intravenously or intracardiac). Patients with ventricular fibrillation or asystole did not respond as well to the calcium administration.

Two other authors, Gando in 1988 and Stueven in 1985, also found questionable benefit on the use of calcium in CPCR. In his randomized controlled study, Stueven found that intravenous calcium appeared to be beneficial in a group of patients with PEA that had a widened QRS complex. Gando did not demonstrate a significant benefit in using intravenous calcium in human patients with CPA although this study was not randomized.

Many more studies demonstrate the ineffectiveness of calcium salts during CPCR. Stueven in 1983, 1984 and1985 was able to demonstrate that calcium salts were ineffective in patients with CPA. The 1983 and 1984 studies retrospectively evaluated the use of calcium in prehospital cardiac arrest and did not find any differences between individuals with PEA and asystole. The 1985 study prospectively evaluated the use of calcium in refractory asystole and did not find any beneficial effects. Walraven (1998) also failed to demonstrate a positive association with the use of calcium in CPCR in human patients.

Two experimental studies evaluated the use of calcium salts in dogs. Blecic (1987) compared the effect of intravenous epinephrine, 5% dextrose in water or calcium chloride in dogs with PEA after ventricular fibrillation. Calcium chloride was determined to be ineffective in its use alone. The use of calcium chloride was no better than using 5% dextrose in water in this group of dogs. Meuret (1984) compared the use of epinephrine to calcium in dogs with CPA. Epinephrine was shown to be superior to calcium and the routine use of calcium was not recommended during CPCR.

Due to the limited and unimpressive studies, routine administration of calcium was not recommended in the 2010 American Heart Association Cardiopulmonary Resuscitation guidelines. There are no studies evaluating the use of calcium in the resuscitation of patients that were hypocalcemic before CPA.

7. Conclusion

Three studies (all LOE 6) show questionable benefit to the use of calcium in human patients with cardiopulmonary arrest. Four studies (LOE 6) show that calcium salts are not recommended in use in human studies with CPA while 2 research studies (LOE 1 and LOE 3) confirm the same findings in dogs. There were no studies that documented a clear positive benefit of administering calcium salts during CPCR. There are no clinical trials regarding calcium administration during CPR to dogs or cats with spontaneous CPA.

Based on the limited number of studies demonstrating a benefit in the administration of calcium, the routine use of calcium is not recommended in CPCR in human patients. There are even more limited animal studies and no clinical veterinary studies evaluating the use of calcium in CPCR in veterinary patients. While it is difficult to extrapolate, it is unlikely that routine administration of calcium will change the outcome of veterinary patients suffering CPA. There may be a role for calcium administration in dogs or cats with CPA and known preexisting hypocalcemia, but this has not been specifically studied.

8. Acknowledgement

9. Citation list

Blecic, S., Backer, D. D., Huynh, C. H., Deleuze, M., Domb, M., Luypaert P. & Vincent, J.-L. 1987. Calcium chloride in experimental electromechanical dissociation: A placebo-controlled trial in dogs. Critical Care Medicine, 15, 324-327.

LOE 1 Opposing (fair)

While calcium administration has been recommended in CPR, its beneficial effects have been challenged. The effectiveness of calcium chloride was evaluated and compared with epinephrine during successive episodes of electromechanical dissociation (EMD) after ventricular fibrillation in closed-chest dogs. Each of three successive episodes of CPR was randomly and blindly treated by repeated (every 2 min) injections of 5 ml H_2O plus either 500 mg of calcium chloride ($CaCl_2$), 1 mg of epinephrine (Epi), or 5% dextrose (D5W). Of 42 CPR attempts performed on 16 dogs, 16 were reversed by only chest compression and artificial ventilation. For the 26 CPR with pharmacologic intervention, recovery was obtained after one injection in 5 of 6 Epi but only in 4 of 11 $CaCl_2$ and 4 of 9 D5W. Only four CPR attempts were ultimately unsuccessful, all in $CaCl_2$ group. During recovery, the Epi group showed significantly higher arterial pressures and heart rates but less severe acidemia. In this model, calcium chloride alone is ineffective during EMD.

Gando S, Tedo I, Tujinaga H, Kubota J.Variation in serum ionized calcium on cardiopulmonary resuscitation. Journal of Anesthesia Volume 2, Number 2, 154-160, DOI: 10.1007/s0054080020154

LOE 6 Neutral (poor)

Changes in serum ionized calcium (Ca^{++}) levels during cardiopulmonary resuscitation (CPR) and before and after CaCh administration have been examined and investigated in 30 patients with cardiopulmonary arrest on arrival (dead on arrival patients) when a significant negative correlation was found to exist between the transportation time and aCa^{++}, as the aCa^{++} level decreased with an increase in the transportation time. Upon arrival, the pH had fallen due to acidosis so that aCa^{++} and cCa^{++} levels were virtually normal. After admission, the pH rose as a result of CPR, resulting in a significant drop in both Ca^{++} levels, so that in most cases resuscitation was not possible. Those successfully resuscitated took over 60 min to return to normal Ca^{++} levels. Administration of approximately 6.6 mg/kg of $CaCl_2$ led to

significant increases in aCa++ and cCa++ to essentially normal levels, even with some patients recording extremely elevated Ca levels, even with some patients recording extremely elevated Ca levels. However, the success rate of resuscitation was not found to show any significant difference according to whether CaCl2 had or had not been administrated.
Thus, it is felt neccessary to re-examine the use of calcium chloride on CPR.

Harrison EE, Amey BD. The use of calcium in cardiac resuscitation. Am J Emerg Med. 1983; 1: 267-73

LOE 6, Neutral (poor)

All records of cardiac arrest patients presenting to the Tampa EMS system for the 24-month period of January, 1980, through December, 1982, were reviewed. Paramedics were given direct orders or standing orders to administer calcium intravenously or intracardiac in patients in ventricular fibrillation, asystole, or electromechanical dissociation. Of the 480 patients receiving calcium for the above conditions, only patients with electromechanical dissociation responded to calcium. Twenty-seven EMD patients responded positively with the immediate return of blood pressure and pulse. Fourteen of these patients arrived at the emergency department with stable vital signs; there were three long-term survivors. Adverse rhythm or rate changes were not noted following calcium use, and arrhythmias associated with digitalis excess were not seen in a small group of patients taking digoxin. Although long-term survivors are limited in this group of patients, positive hemodynamic responses were seen following calcium chloride administration in 10% of EMD patients and not at all in patients with asystole or ventricular fibrillation.

Meuret GH, Schindler HF, Scholler KL. Is calcium indicated in resuscitation? Experimental studies in dogs. Anaesthesist. 1984; 33:108-14

LOE 3 Opposing (fair)

This study compares the effect of epinephrine (11 dogs) with that of the combination of epinephrine with calcium (10 dogs) in CPR after anoxial cardiac arrest. In the epinephrine group resuscitation was successful in all 11 dogs within 4 minutes. In the calcium group only 7 out of 10 dogs could be resuscitated: 3 dogs died during CPR in cause of irreversible fibrillation (2 cases) and "stone heart" (1 case). High CPK-activity reflected severe myocardial cell damage. In the survivors of the calcium group cardiac function was significantly impaired: 1. decreased left ventricular pressure (LVP) and contractility (dp/dt max), 2. increased afterload, 3. decreased cardiac output inspite of increased heart rate, 4. as a consequence, reduced perfusion of the vital organs. - These results foster the conclusion that calcium should not be used henceforth in CPR. Epinephrine was and is still the drug of choice in resuscitation after cardiac arrest.

Stueven H, Thompson BM, Aprahamian C, Darin JC. Use of calcium in prehospital cardiac arrest. Ann Emerg Med. 1983; 12: 136-9.

LOE 6, Opposing (poor)

All records of patients presenting to the Milwaukee County Paramedic System for the period of January 1 to December 31, 1980 were reviewed retrospectively. One hundred seventy-nine patients initially presented in asystole, and 116 patients initially presented in electromechanical dissociation (EMD). All patients with trauma and poisoning were excluded. The in-field successful resuscitation rates for asystole were 8/105 (8%) in the calcium group versus 8/24 (33%) in the no-calcium group ($P < .002$); for EMD they were 10/63 (16%) in the calcium group versus 8/18 (44%) in the no-calcium group ($P < .02$). A successful resuscitation is defined as the conveyance of a patient to the emergency department with a pulse and cardiac rhythm. There were no significant differences between the calcium and no-calcium groups in both the asystole and EMD patients. The use of calcium in the prehospital setting in the currently recommended dosage for cardiac arrest with initial arrest rhythms of asystole and EMD is highly suspect.

Stueven HA, Thompson B, Aprahamian C, Tonsfeldt DJ, Kastenson EH. Calcium Chloride: Reassessment of use in asystole. Ann Emerg Med. 1984; 13:820-2.

LOE 6, Opposing (good)

Calcium chloride has been advocated since the 1920s for resuscitation of asystole and ventricular fibrillation. Most reports have been anecdotal, and have failed to substantiate its effectiveness. In two large retrospective series with a collective experience of 181 patients, investigators reviewed the effectiveness of calcium chloride in asystole and did not support its use. A prospective, randomized, doubleblind study comparing calcium chloride with saline in the prehospital setting was done. Patients with trauma or pediatric arrests were excluded. During the period from October 1982 to October 1983, a total of 32 patients with witnessed arrests presented with a rhythm of asystole and were refractory to epinephrine, bicarbonate, and atropine. The rate of successful resuscitation in the calcium group was 5.6% (1/18), and there were no successful resuscitations (0/14) in the saline group ($P = .37$). A successful resuscitation was defined as conveyance of a patient with a rhythm and pulse to an emergency department. Groups were analyzed for sex, age, cardiac history, and cardiac drugs, and there were no statistically significant differences. No patient who was successfully resuscitated in the field was discharged alive from the hospital. Calcium chloride is of no value in resuscitating refractory asystole in the prehospital cardiac arrest setting.

Stueven HA, Thompson B, Aprahamian C, Tonsfeldt DJ, Kastenson EH. The effectiveness of calcium chloride in refractory electromechanical dissociation. Ann Emerg Med. 1985; 14:626-9

LOE 6, Neutral (good)

The effectiveness of calcium in electromechanical dissociation (EMD) has been challenged. Retrospective studies have been contradictory. To determine its effectiveness a prospective, randomized, blinded study comparing calcium chloride and saline in refractory EMD was carried out in the pre-hospital setting from October 1982 to October 1983. Only patients who had received epinephrine and bicarbonate and were refractory were entered in the study. All trauma and pediatric arrests were excluded. Ninety patients presented in refractory EMD. Overall, eight of 48 who received calcium were resuscitated successfully in the field; two of 42 who received saline were resuscitated succesfully ($P < .07$). A successful resuscitation was defined as the conveyance of a patient with a pulse and a rhythm to an emergency department. Patients were analyzed for age, sex, and witnessing of arrest. There was no statistical difference in demographic data. When the group of EMD patients was broken down into subgroups based on the width of QRS, it was noted that patients with a QRS width less than 0.12 did not respond to calcium, whereas the successfully resuscitated in the group with widened QRS or ischemic changes ($N = 70$) was eight of 39, compared with

one of 31 not receiving calcium (P < .028). Only one patient who was resuscitated successfully was discharged from the hospital alive. Calcium has been shown to be effective in the cardiac resuscitation of patients in refractory EMD. There may be a subset of patients with widened QRS complexes or ischemic changes who will benefit to a greater extent from the use of calcium chloride.

Stueven HA, Thompson B, Aprahamian C, Tonsfeldt DJ, Kastenson EH. Lack of effectiveness of calcium chloride in refractory asystole. Ann Emerg Med. 1985; 14:630-2.

LOE 6, Opposing (good)

The effectiveness of calcium chloride in aystole has been challenged; retrospective studies have not supported its use. We conducted a prospective, randomized, blinded study comparing the effectiveness of calcium chloride with saline in the prehospital paramedic setting. Seventy-three patients who had received epinephrine, bicarbonate, and atropine and were in refractory asystole were included in the study, which was conducted from October 1982 to October 1983. Traumatic and pediatric arrests were excluded. The successful resuscitation rate was three of 39 in the calcium group versus one of 34 in the saline group (P < .37). A successful resuscitation was defined as the conveyance of a patient with a pulse and a rhythm to an emergency department. Groups were analyzed for sex, age, and witnessed arrests. There was no statistically significant difference between the groups. No patient who was resuscitated successfully in the field was discharged from the hospital alive. We conclude that calcium chloride is not of value in resuscitating patients from refractory asystole in the prehospital cardiac arrest setting.

Walraven CV, Stiell IG, Wells GA, Hebert PC, Vandemheen K. Do Advanced Cardiac Life Support Drugs Increase Resuscitation Rates From In-Hospital Cardiac Arrest? 1998. Annals of Emergency Medicine, 32, 544-553.

LOE 6, Opposing (good)

The benefit of Advanced Cardiac Life Support (ACLS) medications during cardiac resuscitation is uncertain. The objective of this study was to determine whether the use of these medications increased resuscitation from in-hospital cardiac arrest. Methods: A prospective cohort of patients undergoing cardiac arrest in 1 of 5 academic hospitals was studied. Patient and arrest factors related to resuscitation outcome were recorded. We determined the association of the administration of ACLS drugs (epinephrine, atropine, bicarbonate, calcium, lidocaine, and bretylium) with survival at 1 hour after resuscitation. Results: Seven hundred seventy-three patients underwent cardiac resuscitation, with 269 (34.8%) surviving for 1 hour. Use of epinephrine, atropine, bicarbonate, calcium, and lidocaine was associated with a decreased chance of successful resuscitation (P <.001 for all except lidocaine, P <.01). While controlling for significant patient factors (age, gender, and previous cardiac or respiratory disease) and arrest factors (initial cardiac rhythm, and cause of arrest), multivariate logistic regression demonstrated a significant association between unsuccessful resuscitation and the use of epinephrine (odds ratio .08 [95% confidence interval .04–.14]), atropine (.24 [.17–.35]), bicarbonate (.31 [.21–.44]), calcium (.32 [.18–.55]), and lidocaine (.48 [.33–.71]). Drug effects did not improve when patients were grouped by their initial cardiac rhythm. Cox proportional hazards models that controlled for significant confounders demonstrated that survivors were significantly less likely to receive epinephrine (P <.001) or atropine (P <.001) throughout the arrest. Conclusion: We found no association between standard ACLS medications and improved resuscitation from in-hospital cardiac arrest. Randomized clinical trials are needed to determine whether other therapies can improve resuscitation from cardiac arrest when compared with the presently used ACLS drugs. [van Walraven C, Stiell IG, Wells GA, Hébert PC, Vandemheen K, for the OTAC Study Group: Do Advanced Cardiac Life

Support drugs increase resuscitation rates from in-hospital cardiac arrest? Ann Emerg Med November 1998;32:544-553.]