

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 cardiac arrest (P), does the use of tracheal drug delivery (I) compared to intravenous drug delivery (C) worsen patient outcome (e.g. ROSC, survival to hospital discharge (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

-MESH via PUBMED

1. cardiopulmonary resuscitation + pediatric
2. intratracheal medications
3. success CPR pediatrics

-CAB Abstracts

1. advanced life support

-Google Scholar

1. intratracheal drug administration
2. advanced life support
3. cardiopulmonary resuscitation + veterinary

4b. Other sources

References within other veterinary CPR articles

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

Inclusion criteria

Methods of CPR

Success rates, veterinary and pediatric CPR

Intratracheal drug delivery (epinephrine, vasopressin)

Review articles

Retrospective and Prospective studies

Exclusion criteria

Chapters, editorials; no mention of response to intratracheal administration of medications used for CPR

4d. Number of articles/sources meeting criteria for further review: 18

Hofmeister, JAVMA 2009, July 37(7)
Plunkett JVIM 2008, Jan-Feb 22(1)
Manisterski, Anesth Analgesia 2002, October 95(4)
Efrati Resuscitation 2001, Aug 50(2)
Parent, Resuscitation, 1999, June 41(1)
Bleske Ann Emerg Med, 1992, Sept 21(9)
Cole, JVECC 2002, Pt I and Pt II
Haldane, Compendium 2004, 26(10)
Waldrop JVECC 2004 14(1)
Ralston, Ann Emerg Med 1985, 14(11)
Mielke, Resuscitation, July 2001, 50(1)
McNamara, Am J of Emerg Med, 1986, 4(1): case report
Raehl, Clin Pharm 1986, July 5(7)
Kleinman, Crit Care Med, Dec 1999, 27(12)
Paret, Resuscitation 1997, 35(1)
Greenberg, Resuscitation 1984, 12(3)
Hahnel, Resuscitation 1989, 17(3)
Hornchen, Crit Care Med 1987, 15

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

Good			Paret, E=pharmacokinetics (IV vs. IT) Manisterski, E=increased bp w/IT, 10x IV dose			<i>Hornchen, A=IV and IT epi vs. no drug</i>
Fair			Efrati, E=increased bp with IT vasopressin Paret, E=increased HR and increased blood levels, IT atropine			<i>Mielke, E=increased bp comparable between IV and IT</i>
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				Hofmeister, A=no difference based on route of drug administration		
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 Opposing Clinical Question

Good						
Fair						
Poor						<i>Kleinman, E=plasma epi levels; found no increase in plasma levels when given IT</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

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

There were no studies examining the specific question that intratracheal (IT) drug delivery worsens patient outcome when compared to the intravenous route.

Paret et al (*Resuscitation*, 1997) studied the pharmacokinetics of IT epinephrine at different doses, in a LOE 3, experimental study. Doses were diluted to 1, 2, 5, and 10 ml, in five anesthetized dogs, with one serving as a control. This was a crossover study, with a one week washout period between dose changes. It was found that mean plasma drug levels significantly increased within 15 seconds of IT administration, for all volumes. The time to maximal concentration and the coefficient of absorption was higher in both the 5 and 10 ml diluents groups. In conclusion, the study supported diluting epinephrine in 5 ml of saline when delivered IT, as absorption and maximum concentration is improved. In addition, it was found that oxygenation and ventilation were not affected when using the 5 and 10 ml volume of diluent to deliver the epinephrine IT.

Manisterski et al (*Anesth Analg*, 2002) tested the effects of 4 different doses of IT epinephrine in an experimental study, LOE 3. Doses of 0.02, 0.035, 0.1, 0.2, and 0.3 mg/kg were administered IT to five anesthetized dogs, with one saline control. It was found that all doses, a significant decrease in systolic, diastolic, and mean blood pressure occurred initially, compared to the saline control. Only the 0.3 mg/kg dose caused a subsequent increase in blood pressure that lasted about 10 minutes. In conclusion, only when the dose administered IT was 10 times the recommended IV dose (0.3 mg/kg) did an increase in blood pressure occur.

Hornchen et al (*Crit Care Med*, 1987) performed an experimental study, LOE 6, in which 24 pigs were administered IT, IV, or no epinephrine after ventricular fibrillation was induced. The IT epinephrine was dosed at 0.1 mg/kg and diluted in 10 ml of normal saline prior to administration. The IV dose of epinephrine was 0.01 mg/kg. All 16 animals that received epinephrine, either IT or IV, had ROSC. Despite internal cardiac massage and artificial ventilation, ROSC was not successful in all 8 pigs in the control group. There was no difference in hemodynamic variables between the IV and IT groups. In conclusion, IT administration of epinephrine performed similarly to IV administration, and was recommended as an alternative route of administration in patients without IV access (i.e., out-of-hospital arrest).

Efrati et al (*Resuscitation*, 2001) performed a LOE 3, experimental study to evaluate the effect of IT vasopressin in five anesthetized dogs. In dogs who received IT vasopressin at 1.2 U/kg, systolic, mean, and diastolic blood pressures increased and heart rate decreased compared to saline controls. These effects were sustained for 60 minutes. In conclusion, this study found that IT vasopressin was absorbed rapidly into the systemic circulation and resulted in expected hemodynamic changes.

Paret et al (*Resuscitation*, 1999), in a LOE 3, experimental study, evaluated the pharmacokinetics of atropine administered IT vs. endobronchially. This study concluded that administering atropine via the endobronchial route (by wedging an intra-cath into a peripheral bronchus) resulted in significantly higher serum concentrations of atropine vs. the dose administered IT. In addition, IT atropine only reached half the maximal blood levels as compared to endobronchial administration.

Mielke et al (*Resuscitation*, 2001) evaluated the effects of epinephrine administered either IV or via 3 different methods IT, in a LOE 6 study. The three methods included administration at the upper end of the tracheal tube, endobronchially via an intracath, or via a special tracheal application tube called the EDGAR tube. The EDGAR tube is an endotracheal tube with an application channel within the wall of the tube, with the port ending at the distal end of the tracheal tube. This study concluded that there was no significant difference between the three methods of intra-tracheal administration of epinephrine when comparing plasma epinephrine concentrations, mean arterial pressures, and end-tidal CO₂ measurements. IV epinephrine resulted in higher plasma epinephrine levels compared to the IT routes.

In a prospective, LOE 4 study examining prognostic indicators for dogs and cats with cardiopulmonary arrest treated by CPR (Hofmeister et al, *JAVMA*, 2009), ROSC was not found to be significantly different

based on route of drug administration. Drugs were administered via a peripheral catheter in 134 of 204 animals, via a central venous catheter in 37 of 204 animals, and IT in 24 of 204 animals. Some animals received drugs via more than one route.

Kleinman et al (Crit Care Med, 1999) examined the efficacy of IV vs. IT administration of epinephrine, in a LOE 6 experimental study in 40 newborn pigs. All pigs were anesthetized, and then ventricular fibrillation was induced, followed by CPR and administration of epinephrine either into the right atrium, femoral vein, or endotracheal tube. The dose of epinephrine for all routes was 0.01 mg/kg. The IT dose was diluted into 2 ml of normal saline and delivered via a 5-Fr feeding tube to the end of the endotracheal tube. It was found that the IT dose did not result in drug delivery to the systemic circulation in these pigs; however, the dose used was lower than what is recommended based on previous experimental studies and results.

7. Conclusion

No studies were found that compared survival as an outcome when drugs are administered IT vs. IV in animals during CPR. Most studies examined plasma levels of drugs when given IT, and dose ranges to achieve sufficient blood levels.

Based on this literature review, IT drugs do achieve blood levels, but some, i.e. epinephrine, must be given at 10 times the IV dose. In addition, diluting the medications with normal saline improves distribution of the drug into the tracheobronchial tree. Administration via a catheter past the endotracheal tube seemed to be the best method of IT drug delivery.

8. Acknowledgement

None

9. Citation list

1. Hofmeister EH, Brainard BM, Egger CM et al. Prognostic indicators for dogs and cats with cardiopulmonary arrest treated by cardiopulmonary cerebral resuscitation at a university teaching hospital. *J Am Vet Med Assoc* 2009;235:50-57
2. Mielke LL, Lanzinger MJ, Aschke C. Plasma epinephrine levels after epinephrine administration using different tracheal administration techniques in an adult CPR porcine model. *Resuscitation* 2001;50:103-108
3. Paret G, MAzkereth R, Sella R et al. Atropine pharmacokinetics and pharmacodynamics following endotracheal versus endobronchial administration in dogs. *Resuscitation* 1999;41:57-62
4. Efrati O, Barak A, Ben-Abraham R. Hemodynamic effects of tracheal administration of vasopressin in dogs. *Resuscitation* 2001;50:227-232
5. Hornchen U, Schuttler J, Stoeckel H et al. Endobronchial instillation of epinephrine during cardiopulmonary resuscitation. *Critical Care Medicine* 1987;15:1037-1039
6. Manisterski Y, Vaknin Z, Ben-Abraham R et al. Endotracheal epinephrine: A call for larger doses. *Anesth Analg* 2002;95:1037-1041
7. Paret G, Vaknin Z, Ezra D et al. Epinephrine pharmacokinetics and pharmacodynamics following endotracheal administration in dogs: the role of volume of diluent. *Resuscitation* 1997;35:77-82
8. Kleinman ME, Oh W, Stonestreet BS. Comparison of intravenous and endotracheal epinephrine during cardiopulmonary resuscitation in newborn piglets. *Crit Care Med* 1999;27(12):2748-2754
9. Waldrop JE, Rozanski EA, Swanke ED et al. Causes of cardiopulmonary arrest, resuscitation management, and functional outcome in dogs and cats surviving cardiopulmonary arrest. *J Vet Emerg Crit Care* 2004;14(1):22-29

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11. Cole SG, Otto CM, Hughes D. Cardiopulmonary cerebral resuscitation in small animals – a clinical practice review. Part II. *J Vet Emerg Crit Care* 2003;13(1):13-23