Post-resuscitation effects of administration of Epinephrine during a cardiac arrest
Paramedic Mini CAT – Fanshawe College Date of review: 11.03.2021

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Clinical Scenario:
EMS dispatched to a hair salon in Collingwood, Ontario for a 62 year old female in cardiac arrest. CPR was not started by any bystander and EMS arrived within 8 minutes. CPR was immediately started, defib pads were attached, and rhythm was analyzed. ECG revealed a ventricular fibrillation rhythm, therefore a shock was delivered and epinephrine was administered. After another 2 minutes of CPR, the ECG showed sinus bradycardia. Your partner preps the stretcher to get ready for transport as you continue to ventilate the patient. As you are en route to the hospital, you wonder what the post-resuscitation effects of administering epinephrine during an out of hospital cardiac arrest are.

Background
Epinephrine has been used as a treatment for cardiac arrest for over 50 years. However, there is little research on the effects of epinephrine post-resuscitation. Epinephrine is an a-adrenergic receptor, where it constricts arterioles to increase aortic diastolic pressure. Therefore, it augments coronary blood flow and increases the chance of a return of spontaneous circulation. On the other hand, a-adrenergic stimulation causes platelet activation and in turn promotes thrombosis and impairs the microvascular blood flow in the cerebral cortex. This increases the severity of cerebral ischemia during CPR and after a return of spontaneous circulation.

The literature researches the timeliness of when epinephrine was administered, effects on cerebrovascular, systemic hemodynamics, and neurological outcomes.

Review question
PICO: Population, Intervention, Comparison, Outcome

P: in prehospital cardiac arrest patients
I: does epinephrine
C: versus no epinephrine
O: effects on patient outcome post resuscitation

Search strategy (Basic): “paramedic or ems or prehospital” and “cardiac arrest or cardiopulmonary resuscitation or cpr or resuscitation” and “epinephrine or adrenaline”
Limits: Studies after 2017 that are English written.
Databases searched: Google Scholar and Mendeley

Search results: 51
Included for review: Four studies were reviewed as they were published recently; 2018, 2019, 2020. Additionally, the studies are primary sources rather than secondary sources. The studies’ population included children and adults. All studies measured the association between administration of epinephrine and return of spontaneous circulation along with effects post-resuscitation.

Title, author, year	Study design & LOE	Population	Intervention	Outcomes	Results	Weaknesses & Strengths
Time to epinephrine treatment is associated with the risk of mortality in children who achieve sustained ROSC after traumatic out of hospital cardiac arrest Yan-Ren Lin, Meng Huan Wu, Tren-Yi Chen, Yuan-Jhen Syue, Mei-Chueh Yang, Tsung-Han Lee, Chih-Ming Lin, Chu-Chung Chou, Chin-Fu Chang, Chao-Jui Li Published: March 2019	Multicenter retrospective study from January 1, 2003 to December 31, 2014. Children were classified into hemorrhagic shock (blood loss >30% of total body fluid) and non-hemorrhagic shock. LOE-3	Children aged 19 or younger who experienced traumatic out of hospital cardiac arrest (OHCA) and were administered epinephrine for resuscitation were included. 509 children with traumatic OHCA admitted to the Emergency Department. Trauma mechanisms that included intoxication, drowning, or burn injury were not included.	Children were classified into hemorrhagic shock (blood loss >30% of total body fluid) and non-hemorrhagic group. The time of epinephrine treatment, patient characteristics, and major mechanism of arrest were analyzed retrospectively and correlated with outcomes.	The primary outcome is achievement of sustained ROSC (lasting longer than 20 minutes), survival to discharge, and good neurological outcomes. Early epinephrine treatment was significantly associated with achieving sustained ROSC in both the hemorrhagic shock and non-hemorrhagic shock group. Although sustained ROSC was achieved in 147 and 75 children, most of them still died during the hospital stay. Early epinephrine treatment was no significantly associated with survival to discharge	Early epinephrine administration was significantly associated with achieving sustained ROSC in both children with hemorrhagic shock and non-hemorrhagic shock traumatic OHCA. For children with hemorrhagic shock, early epinephrine administration was associated with both beneficial and harmful effects during the post-resuscitation period.	Determining the amount of prehospitalization hemorrhage was a major limitation as it could potentially be underestimated. Additionally, association of early epinephrine administration with mortality could have explained early survival bias. Early survival did not guarantee long-term survival and could also be a survival bias. Study period started with 568 children admitted to 3 medical centers. There were 35 children that did not receive any epinephrine or resuscitation treatment. 29 out of the 35 were pronounced dead. The other 6 patients achieved

				or good neurological outcomes. The secondary outcome is the duration of survival and initial post-resuscitation hemodynamic status. Early epinephrine treatment was significantly related to a better initial GCS score. Early and middle epinephrine administration were both significantly associated with tachycardia, while early epinephrine administration showed a slightly higher proportion of normotensive patients.		ROSC without administration of epinephrine. Therefore, the study included 509 children and detailed what happened to the other 35 children. $P < 0.05$ typically indicates strong evidence to statistically support the outcome of both beneficial and harmful effects of epinephrine administration during the post-resuscitation period.

The influence of time to adrenaline administration in the Paramedic 2 randomised controlled trial Gavin Perkins, Claire Kenna, Chen Ji, Charles Deakin, Jerry Nolan, Tom Quinn, Charlotte Scomparin, Rachael Fothergill, Imogen Gunson, Helen Pocock, Nigel Rees, Lyndsey O'Shea, Judith Finn, Simon Gates, Ranjit Lall Published: January 2020	PARAMEDIC2: large randomised, double blind, placebo controlled trial which evaluated the effect of standard dose adrenaline in adults with out of hospital cardiac arrest by five National Health Service ambulance services in the United Kingdom from December 2014 to October 2017. LOE-1	Adult patients treated for out of hospital cardiac arrest who were not successfully resuscitated by means of defibrillation or CPR and met the predetermined eligibility criteria. Sample size is 8016, 4902 sustained a witnessed cardiac arrest-2437 received placebo and 2465 received adrenaline.	Patients treated for out of hospital cardiac arrest who were not successfully resuscitated by means of defibrillation or CPR, and who met predetermined eligibility criteria, were randomly allocated to receive parenteral adrenaline or saline placebo. There were 10ml syringes loaded with either ten 1 mg doses of adrenaline or ten doses of 0.9% saline. The trial packs and their content were identical in appearance	Those who received drug administration immediately after cardiac arrest was twice more likely to have ROSC compared to placebo. ROSC decrease at a greater rate in the placebo arm compared with the adrenaline arm. The increase of timing of drug administration increases, the odds ratio of ROSC increases between the adrenaline and placebo group by a factor of 1.03 for every additional minute. The probability of ROSC for those given adrenaline immediately after cardiac arrest were 0.46 compared to	The rates of ROSC on arrival at hospital, survival and favourable neurological outcome all decreased as the interval from cardiac arrest to the administration of drug or placebo increased. The rate of survival and favourable neurological outcomes was not substantively different over time between the adrenaline and placebo group.	A strength of this study is that it focused on reducing bias (doubled blind and placebo). One weakness is the post-resuscitation care treatments such as temperature management, haemodynamic and ventilator management, percutaneous coronary intervention, and prognostication, were not strictly protocolized or monitored. Therefore, it is possible that different approaches to post-resuscitation care may have influenced longer term outcomes. Another weakness is there were no comparative (higher or lower) dosage of epinephrine administered, which could have produced different results.

			and carried a unique identification number.	0.3 for those given placebo. The rate of survival to 30 days decreases as time to treatment increases in both the placebo and adrenaline group.		With a p <0.001 for favourable neurological outcome at discharge, therefore the results are statistically significant.
A randomized trial of Epinephrine in Out of Hospital Cardiac Arrest Gavin Perkins (MD), Chen Ji (PhD), Charles Deakin (MD), Tom Quinn, M.Phil, Jerry Nolan, Charlotte Scomparin, Scott Regan, John Long, Anne Slowther, Helen Pocock,	Multicenter, randomized, double-blind placebo-controlled PARAMEDIC2 trial conducted by 5 National Health Services ambulance services to United Kingdom. LOE-1	Adult patients who had sustained an out of hospital cardiac arrest for which advanced life support was provided. Criteria for exclusion include known or apparent pregnancy, age of less than 16 years old, cardiac arrest from anaphylaxis or asthma, or administration of epinephrine	If initial attempts at resuscitation were unsuccessful, the patient was randomly assigned to receive either parenteral epinephrine or saline placebo. There were identical-appearing trial packs containing 10 prefilled syringes, with each syringe containing either 1mg of	The primary outcome was the rate of survival at 30 days. The secondary outcome were the rate of survival until hospital admission, the lengths of stay in the hospital and in the intensive care unit, the rates of survival at hospital discharge at 3 months, and the neurologic outcomes at hospital discharge at 3 months. In the epinephrine group, 130 patients were alive at 30 days, compared to	The use of epinephrine during resuscitation for out of hospital cardiac arrest resulted in a significantly higher rate of survival at 30 days than the use of placebo. Patients in the epinephrine group had a higher rate of return of spontaneous circulation, a higher	One weakness of this study includes not incorporating strategies that could have produced different results; different dose or dosing intervals. Another weakness if the information regarding the patient's baseline neurologic status was not collected, and information regarding the quality of CPR was limited to the first 5 minutes of cardiac arrest. The study started with 8103 patients, however

John Black, Fionna Moore, Rachael Fothergill, Nigel Rees, Lyndsey O'Shea, Mark Docherty, Imogen Gunson, Kyee Han, Karl Charlton, Judith Finn, Stavros Petrou, Nigel Stallard, Simon Gates, Ranjit Lall, Published: July 18, 2018		before the arrival of the trial-trained paramedic. Traumatic cardiac arrest were also excluded. There was a total of 8014 patients.	epinephrine or 0.9% saline. The randomized sequence was computer-generated by the minimization method with an overall assignment ratio of 1:1.	94 patients in the placebo group. There was no significant difference between the epinephrine group and the placebo group for patients who survived until hospital charge with favourable neurologic outcomes. Severe neurological impairment were more common among survivors in the epinephrine group than in the placebo group.	frequency of transport to the hospital, and a higher rate of treatment in the ICU. There were no favourable neurological outcomes seen in either groups.	87 patients were ineligible to participate and 2 patients had unknown trial-group assignments due to missing trial-pack numbers.
Impact of epinephrine administration frequency in out of hospital cardiac arrest patients: a retrospective analysis in a tertiary	Retrospective Analysis in a tertiary hospital setting – 300 records for out of hospital cardiac arrest in Saudi Arabia at King Fahd University Hospital from 2005 to 2015.	Adult patients >18 years old, cardiac arrest either traumatic or non-traumatic, and patients who received CPR either before arriving	178 received epinephrine dose more than 15 minutes after ED arrival, 24 received the dose within 11 to 15 minutes, 35 received	Epinephrine doses were administered significantly more frequently in out of hospital cardiac arrest non-survivors compared with survivors.	Further studies are needed to investigate whether the long-term outcomes of out of hospital cardiac arrest patients are	One limitation to this study was that it was an observational study that lacked randomization, therefore cannot establish causation. Time and frequency of epinephrine administration were

hospital setting Mohammed Al-Mulhim, Mohammed Alshahrani, Laila Asonto, Ahmad Abdulhady, Talal Almutairi, Mariam Hajji, Mohammed Alrubaish, Khalid Almulhim, Mariam Al-Sulaiman, and Layla Al-Qahtani Published: 2019	LOE-5	at the hospital or in the ED for at least 5 minutes. Sample size was 300 - 199 men, and 101 were women. Overall age was 50.4 (14-98 years old). Most of the participants were Saudis, while 122 were non-Saudis.	the dose within 6 to 10 minutes of arrival, and 63 received the dose within 0 to 5 minutes of arrival.	Epinephrine is associated with higher 30 day survival rate compared with the placebo group. There was no benefit in the neurological outcome. Early epinephrine administration within 5 minutes was associated with a lower survival rate until hospital discharge.	influenced by the timing and frequency of epinephrine administration.	obtained from the hospital records- which were completed during an emergency, therefore they might not be very accurate because of the emergency situation. CPR was not standardized across all cases, therefore this could have affected the outcome Long term follow up with the patients who survived and were discharged were not analyzed. A strength of this observational study was that it lacked randomization, however can establish an association between epinephrine frequency and patient outcomes. There was a $p<0.0005$, therefore no statistically significant difference

						between the survival and non-survival groups in terms of gender, age, time interval of the first epinephrine dose.

Comments:
Early administration of epinephrine is associated with successful return of spontaneous circulation.

The shorter the time frame to administer epinephrine is associated with more favourable neurological outcome and rate of survival.

Patients in cardiac arrest that were administered epinephrine had a higher rate of return of spontaneous circulation, higher frequency of transport to the hospital, and a higher rate of treatment in the ICU. There was no evidence to show favourable neurological outcomes with or without administration of epinephrine.

Considerations:
One limitations that should be considered when using the evidence from the above review includes the differing populations and population sizes. One study used children aged 19 or younger, adults greater than 16 years old, and adults older than 18 including traumatic and non-traumatic cardiac arrest. This poses a limitation as the age varies between pediatric to 90 years old.

The study sample size varies between all the reviewed studies. The greater the sample size, the more reliable the results, however there is a certain point where the sample size is too large. One study had 509 participants, another study had 4902 participants, the third study had 8014 participants, and the last study had 300. Additionally, the research studies were conducted in different sites- Taiwan, England/Wales, United Kingdom, and Saudi Arabia. This represents the population of where the study was conducted, however, may not reflect the population in South Western Ontario.

Another limitation to consider when attempting to use the evidence outlined in the review is the inability to compare

outcomes before and after a time of administration of epinephrine (eg. 5 minutes). The study by Al-Mulhim et al., showed the results of administration of epinephrine after 5, 10, and 15 minutes, but did not show the outcomes of before administration of epinephrine. Therefore, there was no baseline to compare the results to. Additionally, the study by Perkins et al., had either a placebo or epinephrine administered. In this type of double blind study, there is also some uncertainty if the paramedic administering the treatment is blinded to what they are administering.

There is also poor quality evidence that would limit the use of the evidence for the study by Al-Mulhim et al. This study did not control of identify when exactly cardiac arrest began to justify what the time frames were. This would be difficult as there was no documentation of the time on the emergency hospital records and if there was, there was no way to determine the accuracy of the time.

In all of the studies, the outcomes were all based on the patients that survived cardiac arrest, therefore, it would be difficult to differentiate if it was epinephrine that caused this. All the studies had a survivalship bias as the subjects that died during the cardiac arrest were not used in the data.

In regards to the research paper studying administration of epinephrine to children, the results indicated early epinephrine administration was associated with both beneficial and harmful effects during the post-resuscitation period. However, the amount of blood loss along with the time of initial cardiac arrest to administration of epinephrine could have been underestimated. This would in turn skew the data and results may not be as reliable.

Clinical bottom line:
Early epinephrine administration was significantly associated with achieving sustained ROSC in both children and adults and showed higher rate of survival at 30 days.

Neurological outcomes had no favourable outcome with the use of epinephrine.

References
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#	Query	Limiters/Expanders	Last Run Via	Results
S4	(epinephrine or adrenaline) AND (S1 AND S2 AND S3)	Limiters - Date of Publication: 20180101-20211231 Expanders - Apply related words; Apply equivalent subjects Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE	78
S3	epinephrine or adrenaline	Expanders - Apply related words; Apply equivalent subjects Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE	77,911
S2	cardiac arrest or cardiopulmonary resuscitation or cpr or resuscitation	Expanders - Apply related words; Apply equivalent subjects Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE	110,281
S1	paramedic or ems or prehospital	Expanders - Apply related words; Apply equivalent subjects Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE	31,725