WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care

Worksheet author(s)

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Clinical question.

In adult patients with ROSC after cardiac arrest (prehospital or in-hospital) (P), does the use of a controlled oxygenation strategy (including specific oxygenation goal) (I) as opposed to standard care (C), improve outcome (O) (eg. survival)?

Is this question addressing an intervention/therapy, prognosis or diagnosis? Intervention and prognosis
State if this is a proposed new topic or revision of existing worksheet: new topic

Conflict of interest specific to this question

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

Search strategy (including electronic databases searched).

Search strategy for ILCOR

In adult patients with ROSC after cardiac arrest (prehospital or in-hospital) (P), does the use of a controlled oxygenation strategy (including specific oxygenation goal) (I) as opposed to standard care (C), improve outcome (O) (eg. survival)?

PubMed

I= oxygen
P= cardiac arrest
C= standard care
O= survival/ quality

1.Search heart arrest [mesh] AND Oxygen Inhalation Therapy[mesh] Limits: Humans, English

2.Search heart arrest and neonatal and room air

3. heart arrest neonatal and oxygen
Revised search strategy
Animal studies included
Neonatal excluded unlesst he study was to assess outcome data or biochemical /tissue data from targetted therapy
Search strategy became on Pub med:

Search strategy pub med

I= controlled oxygen strategy
P= cardiac arrest
C= standard Care
O= outcome

SEARCH
Heart arrest = 35465
Sudden cardiac arrest= 17339

Cardiopulmonary resuscitation=10957
Oxygen inhalation therapy= 19839
Search 1 or 2 or 3 and oxygeninhalation therapy= 110
Review abstracts of the 110 = 11 selected
From 11 on article expanded to related articles = Kuisma/boyd = 284 articles
Abstracts of these reviewed 14 items from this list
Hyperoxic resuscitation = 80 articles
Abstracts reviewed from this = 17 articles
Normoxic resuscitation = 61 articles abstracts reviewed= 18
Collections of 14+18+17+11 articles merged so as to remove duplication and 20 articles remained that fitted criteria.
Search widened
Oximetry=11382
Cardiac arrest = 39804
Heart arrest= 34465
Neurological outcome= 18547 Cardiac arrest = 39804 Heart arrest= 34465 Neurological outcome= 18547 terms combined = 7 articles

Abstracts reviewed = 1 Balan IS, Fiskum G, Hazelton J, Cotto-Cumba C, Rosenthal RE.

Related articles = 101 of which abstract review resulted in 11 articles
Combining the collections 20 from the earlier search and 11 from this and removing duplication resulted in 27articles for review

The search was repeated as at 03/09/2009
There were no additional articles fulfilling the previously submitted criteria
When the exclusion criteria were applied there were 11 articles left for review.

EMBASE
'arterial oxygen tension'/exp OR 'oxygen blood level'/exp OR 'oxygen breathing' and 'heart arrest'/exp

COCHRANE
cardiac arrest):ti,ab,kw
(neonatal):ti,ab,kw 5002

#5 MeSH descriptor Oxygen explode all trees with qualifiers: TH,AB,AB 0
#6 MeSH descriptor Heart Arrest explode all trees
#7 MeSH descriptor Infant, Newborn explode all trees 9980
14 MeSH descriptor Cardiopulmonary Resuscitation explode all trees 314

#16 MeSH descriptor Infant, Newborn, this term only with qualifier: TH 0 edit delete

modified to remove mesh descriptor ,infant, newborn

- State inclusion and exclusion criteria

inclusion:
all ages
all adult studies included
animal studies included if the model was of cardiac arrest

Exclusion
Non human- animal studies included on the revised proposal
Traumatic brain injury and the effect of oxygen strategy
Neonatal resuscitation not for cardiac arrest
CPR ventilation to compression strategy with no oxygen strategy after ROSC
Review articles
Studies comparing hyperbaric oxygen with 100% oxygen
Studies showing biochemical outcomes only.
studies presented as abstracts only
studies presented at meetings and forums but not published
studies that did not answer the question comparing oxygen strategies and outcome

- Number of articles/sources meeting criteria for further review:

11 pub med/Cochrane embase

Summary of evidence

In adult patients with ROSC after cardiac arrest (prehospital or in-hospital) (P), does the use of a controlled oxygenation strategy (including specific oxygenation goal) (I) as opposed to standard care (C), improve outcome (O) (eg. survival)?

Evidence Supporting Clinical Question

Good					***Balan 2006E***
Fair					***Masala 1992E*** ***Varenzski2006BE*** ***Zwymer 1994BE*** ***Liu 1998 E*** ***Richards, E. 2007 E*** ***Richards, E. 2006 E***
Poor					
	1	**2**	**3**	**4**	**5**
Level of evidence					

A = Return of spontaneous circulation
B = Survival of event
C = Survival to hospital discharge
D = Intact neurological survival
E = Other endpoint
Italics = Animal studies

Evidence Neutral to Clinical question

Good					
Fair					***Lipinski** 1999 BDE* ***Zwymer 1995ABE****
Poor	**Kruisma 2006 C/D/E****				***Smith 2006 E***
	1	**2**	**3**	**4**	**5**
Level of evidence					

A = Return of spontaneous circulation
B = Survival of event
C = Survival to hospital discharge
D = Intact neurological survival
E = Other endpoint
Italics = Animal studies
** compared normoxia to hypoxia*
**compared 30% Oxygen with 100% oxygen

Evidence Opposing Clinical Question

Good					
Fair					
Poor					
	1	**2**	**3**	**4**	**5**
Level of evidence					

A = Return of spontaneous circulation
B = Survival of event
C = Survival to hospital discharge
D = Intact neurological survival
E = Other endpoint
Italics = Animal studies

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

There is only one LOE1 randomized prospective clinical trial (Kuisma, 2006, 199) which compared ventilation with 30% oxygen or 100% oxygen for the first 60 minutes after ROSC. No statistical difference was detected in serum biomarkers of acute brain injury, survival to hospital discharge, or the percent of patients with good neurological outcome (CPC 1 or 2) at hospital discharge. However, this study was not adequately powered to detect important differences in survival and CPC at hospital discharge. It must be noted that a significant number of the patients (5 of the 14 in the 30% group) required an FIO2 in excess of 30% to maintain arterial oxygen saturations in excess of 95%.

Six studies LOE5 studies (Marsala, 1992, 121; Zwemer, 1994, 159; Liu, 1998, 1679; Vereczki 2006, 821;) support the hypothesis that 100% oxygen can produce a worse outcome than room air.

These showed biochemical and worse functional outcome before or at 24 hours in animal cardiac arrest models when 100% oxygen is compared with room air post ROSC. None of these studies offer any data post the very early period. These studies did not titrate the FIO2 to a measured Oximetry end-point.

One LOE5 animal cardiac arrest study addressed issue of the titration of the FIO2 to an Oximetry endpoint: (Balan 2006, 3008) demonstrated that ventilation with 100% oxygen (generating PaO2 > 350 mm Hg) during the first 15 to 60 minutes after ROSC caused neurodegeneration and worse function neurological outcome when compared to FiO2 titrated to an arterial pulse Oximetry reading between 94% and 96%. This study too is limited by the lack of outcome data post 24 hours.

Only one study examines outcomes at 72 hours. This was a neutral LOE5 animal study (Lipinski, 1999, 221) and did not detect any difference in outcomes at 72 hours when animals were ventilated with 100% oxygen or room air during CPR and for the first hour after ROSC. There are no studies comparing outcomes post 24 hours with 100% oxygen and an FIO2 targeted to an Oximetry end point.

Hypoxic resuscitation in animals has been studied. LOE5 (Zwemer 1995 225) failed to show any difference in outcome when comparing 2 levels of hypoxic FiO2 (0.085 and 0.12) with normoxic resuscitation when given for the intra and early (15 mins) post ROSC period. The study could not demonstrate a significant difference in neurological assessment scores at 72 hours or survival. The study also failed to show a significant difference in the serum biomarkers of oxidant injury.

My conclusion is the Data does not show that there is any evidence against the use of oxygen concentrations of <100% in the immediate ROSC period, at both 24 hours and 72 hours in animals. However there is no data showing a benefit at 72 hours from a restrictive approach.

Given that there is no demonstrated adverse outcome with a restrictive approach and data suggesting there may be a benefit (at least at 24 hours) a properly powered prospective randomized trial is needed to clarify whether titration of Oxygen to arterial saturations in the immediate post ROSC period alters survival from cardiac arrest in a meaningful way is needed.

Acknowledgements:

References:

1.
Author: Balan, I. S.; Fiskum, G.; Hazelton, J.; Cotto-Cumba, C.; Rosenthal, R. E.
Year: 2006
Title: Oximetry-guided reoxygenation improves neurological outcome after experimental cardiac arrest
Journal: Stroke
Volume: 37
Issue: 12
Pages: 3008-13
Date: Dec
Short Title: Oximetry-guided reoxygenation improves neurological outcome after experimental cardiac arrest

ISSN: 1524-4628 (Electronic)
Accession Number: 17068310
COI: no statement
Language: english

Notes: ***LOE=5***
GOOD QUALITY STUDY- comparing neurological defecit score and histologic CA1 pyramidal neuron degredation NORMOXIA PRODUCED SIG BETTER BP AND NEUROLOGICAL OUTCOME

2.
Author: Kuisma, M.; Boyd, J.; Voipio, V.; Alaspaa, A.; Roine, R. O.; Rosenberg, P.
Year: 2006
Title: Comparison of 30 and the 100% inspired oxygen concentrations during early post-resuscitation period: a randomised controlled pilot study
Journal: Resuscitation
Volume: 69
Issue: 2
Pages: 199-206
Date: May
Short Title: Comparison of 30 and the 100% inspired oxygen concentrations during early post-resuscitation period: a randomised controlled pilot study
ISSN: 0300-9572 (Print)
Accession Number: 16500018
COI: statement in paper declaring no COI

Notes: ***LOE= 1 BUT PILOT STUDY ONLY.***
QUALITY = poor
ASSIGNMENT = RANDOMIZED
LIST CONCEALED
ALL PATIENTS ACCOUNTED FOR BUT NO BLINDING
TREATMENT WAS NOT EQUAL- MORE THROMBOLYSIS IN THE 30% GROUP
THE NSE LEVELS WERE HIGHER IN THE 100% GROUP ONLY WHEN NO THERAPUTIC HYPOTHERMIA USED.
THE STUDY WAS NOT POWERED FOR SURVIVAL, ONLY INCLUDED VF ARREST, WITNESSED

3.
Author: Lipinski, C. A.; Hicks, S. D.; Callaway, C. W.
Year: 1999
Title: Normoxic ventilation during resuscitation and outcome from asphyxial cardiac arrest in rats
Journal: Resuscitation
Volume: 42
Issue: 3
Pages: 221-9
Date: Nov
Short Title: Normoxic ventilation during resuscitation and outcome from asphyxial cardiac arrest in rats

ISSN: 0300-9572 (Print)
Accession Number: 10625163
COI: no statement

Notes: ***LOE=5***
quality = fair no sham group no blinding no randomization
the study is neutral to the question posed by ILCOR – showing no histological difference in hippocampal damage, nor any behavioural advantage with targeted FIO2

4.
Author: Liu, Y.; Rosenthal, R. E.; Haywood, Y.; Miljkovic-Lolic, M.; Vanderhoek, J. Y.; Fiskum, G.
Year: 1998
Title: Normoxic ventilation after cardiac arrest reduces oxidation of brain lipids and improves neurological outcome
Journal: Stroke
Volume: 29
Issue: 8
Pages: 1679-86
Date: Aug
Short Title: Normoxic ventilation after cardiac arrest reduces oxidation of brain lipids and improves neurological outcome
ISSN: 0039-2499 (Print)
Accession Number: 9707212
COI: no statement

Notes: ***LOE=5 quality = poor no sham group no blinding no randomization***
animals ventilated with 100% oxygen for 1 hour after a 10 minute cardiac arrest had a poorer neuriologic defecit score at 24 hours post arrest.

5.
Author: Marsala, J.; Marsala, M.; Vanicky, I.; Galik, J.; Orendacova, J.
Year: 1992
Title: Post cardiac arrest hyperoxic resuscitation enhances neuronal vulnerability of the respiratory rhythm generator and some brainstem and spinal cord neuronal pools in the dog
Journal: Neurosci Lett
Volume: 146
Issue: 2
Pages: 121-4
Date: Nov 9
Short Title: Post cardiac arrest hyperoxic resuscitation enhances neuronal vulnerability of the respiratory rhythm generator and some brainstem and spinal cord neuronal pools in the dog
ISSN: 0304-3940 (Print)
Accession Number: 1491777
COI: no statement

Notes: ***LOE=5 quality = fair no blinding no randomization***
The authors report at 4 separate neurological regions and find that 100% oxygen statistically increases the number of dying neurons if used for 1 hour post 15 minutes of cardiac arrest.

6.
Author: Michael Smith, J.; Roberts, W. H.; Miller, J. D.; Hasselfeld, K. A.; Pat Hendy, M.
Year: 2006
Title: Controlled cardiac reoxygenation does not improve myocardial function following global myocardial ischemia
Journal: Int J Surg
Volume: 4
Issue: 3
Pages: 153-9
Short Title: Controlled cardiac reoxygenation does not improve myocardial function following global myocardial ischemia
ISSN: 1743-9159 (Electronic)
Accession Number: 17462339
COI: no statement
Grant: Medical Education And Research Fund Of The Good Samaratin Hospital

Notes: ***LOE=5 quality = poor no sham group no blinding no randomization and the model was of bypass not cardiac arrest and ROSC. Neutral to the Question***
The authors could not find any statistical difference in outcome between normoxia and reperfusion via an incremental controlled increase of PaO2 from 40mm to 110 mmHg over 15 minutes.

7.
Author: Richards, E. M.; Fiskum, G.; Rosenthal, R. E.; Hopkins, I.; McKenna, M. C.
Year: 2007
Title: Hyperoxic reperfusion after global ischemia decreases hippocampal energy metabolism
Journal: Stroke
Volume: 38
Issue: 5
Pages: 1578-84
Date: May
Short Title: Hyperoxic reperfusion after global ischemia decreases hippocampal energy metabolism
ISSN: 1524-4628 (Electronic)
Accession Number: 17413048
COI: no statement

Notes: ***LOE=5 quality = fair no blinding no randomization***
The study compares the changes at the hippocampus and cerebral cortex in animals after 10 minutes of cardiac arrest followed by resuscitation with 100% FIO2 or normoxic Fio2 21-30%
The study showed the hippocampus was significantly more sensitive to hyperoxia.

8.
Author: Richards, E. M.; Rosenthal, R. E.; Kristian, T.; Fiskum, G.
Year: 2006
Title: Postischemic hyperoxia reduces hippocampal pyruvate dehydrogenase activity
Journal: Free Radic Biol Med
Volume: 40

Issue: 11
Pages: 1960-70
Date: Jun 1
Short Title: Postischemic hyperoxia reduces hippocampal pyruvate dehydrogenase activity
ISSN: 0891-5849 (Print)
Accession Number: 16716897
COI: no statement

Notes: ***LOE=5 quality = fair no blinding no randomization***
The study compares the enzyme levels at the hippocampus and cerebral cortex in animals after 10 minutes of cardiac arrest followed by resuscitation with 100% FIO2 or normoxic Fio2 21-30%
The study showed that the hippocampus was significantly more sensitive to hyperoxia compared to the cortex. The normoxic group failed to show any difference between the cortex and hippocampus

9.

Author: Vereczki, V.; Martin, E.; Rosenthal, R. E.; Hof, P. R.; Hoffman, G. E.; Fiskum, G.
Year: 2006
Title: Normoxic resuscitation after cardiac arrest protects against hippocampal oxidative stress, metabolic dysfunction, and neuronal death
Journal: J Cereb Blood Flow Metab
Volume: 26
Issue: 6
Pages: 821-35
Date: Jun
Short Title: Normoxic resuscitation after cardiac arrest protects against hippocampal oxidative stress, metabolic dysfunction, and neuronal death
ISSN: 0271-678X (Print)
Accession Number: 16251887
Grant: NIH grants NS34152 and NS49425 to G Fiscum and AHA grant 0215331 to E martin
COI: no statement

Notes: ***LOE=5 quality = fair no blinding no randomization – supportive evidence***
The study showed a non signioficent trend towards increased CA1 pyrimadal neuron degeneration at 24 hours post 10 minutes asphyxia and 1 hour of either 100% FIO2 or 21% fio2 after ROSC.

Author: Zwemer, C. F.; Whitesall, S. E.; D'Alecy, L. G.
Year: 1994
Title: Cardiopulmonary-cerebral resuscitation with 100% oxygen exacerbates neurological dysfunction following nine minutes of normothermic cardiac arrest in dogs
Journal: Resuscitation
Volume: 27
Issue: 2
Pages: 159-70

Date: Mar
Short Title: Cardiopulmonary-cerebral resuscitation with 100% oxygen exacerbates neurological dysfunction following nine minutes of normothermic cardiac arrest in dogs
ISSN: 0300-9572 (Print)
Accession Number: 8086011
COI: no statement

Notes: ***fair quality supportive evidenceLOE=5 3 treatment arms no blinding no randomization-supportive of the question.***
The neurological defecit at 12 and 24 hours post ROSC in the 100% fio2 treated dogs was significantly worse than those treated with room air FIO2 21%.
The pretreatment with an anti-oxidant agent prior to the induced cardiac arrest in the hyperoxic group produced outcomes no different from the normoxic group

Author: Zwemer, C. F.; Whitesall, S. E.; D'Alecy, L. G.
Year: 1995
Title: Hypoxic cardiopulmonary-cerebral resuscitation fails to improve neurological outcome following cardiac arrest in dogs
Journal: Resuscitation
Volume: 29
Issue: 3
Pages: 225-36
Date: Jun
Short Title: Hypoxic cardiopulmonary-cerebral resuscitation fails to improve neurological outcome following cardiac arrest in dogs
ISSN: 0300-9572 (Print)
Accession Number: 7667554
COI: no statement
Grant: American Heart Association,Upjohn Company,Biotek Instruments Company Physio-Control Corp

Notes: ***LOE=5 poor quality neutral to the question. this study compares survival and neurological deficit scores of Dogs. The dogs had 9 minutes of cardiac arrest then hypoxic FIO2 0.12, hypoxicFIO2= 0.085 or normoxicFIO2=0.21duringCPR and for 15 minutes afterROSC.***
No difference in neurological defecit score was observed at 24 hours.
The study was uinderpowered to demonstrate neurological defecits and survival.
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