EXTRACORPOREAL CARDIOPULMONARY RESUSCITATION (ECPR) VERSUS MANUAL OR MECHANICAL CARDIOPULMONARY RESUSCITATION (CPR) FOR CARDIAC ARREST: A SYSTEMATIC REVIEW

SYSTEMATIC REVIEW PROTOCOL

Version 2.0

March 5, 2018

TITLE

Extracorporeal cardiopulmonary resuscitation (ECPR) versus manual or mechanical cardiopulmonary resuscitation (CPR) for cardiac arrest: a systematic review

REGISTRATION

This protocol was registered at PROSPERO on January 6th, 2018

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AMENDMENTS

Any major modification to the protocol after registration, which may impact the conduct of the study including study eligibility criteria, information sources, search strategy, data management, selection and collection, outcomes, and data synthesis will be agreed upon by all authors listed and added as an amendment. Minor administrative corrections or clarification will require no formal documentation.

Changes from version 1 (January 6, 2018) to version 2 (March 5, 2018):

- Addition of "Studies with ≤ 5 patients receiving ECPR or studies with no timing on ECPR will be excluded." under eligibility criteria.

- Substantial modifications to the “Outcomes” section

FINANCIAL SUPPORT

Funding was provided to Lars W. Andersen from the International Liaison Committee on Resuscitation (ILCOR). There was no other funding.

INTRODUCTION

Rationale

Out-of-hospital cardiac arrest (OHCA) affects over 350,000 individuals in the United States[1], and 275,000 individuals in Europe[2, 3] each year. In-hospital cardiac arrest (IHCA) occurs in an estimated 200,000 patients per year in the United States.[4] Mortality remains high which has led to an increased use of advanced treatments in order to improve outcomes. One of these advanced treatments is extracorporeal cardiopulmonary resuscitation (ECPR) were an extracorporeal circuit is used to achieve circulation during cardiac arrest. The benefits of ECPR are unclear and optimal patient selection and timing is not well-understood. Furthermore, the cost-effectiveness is unclear and ethical considerations related to using and studying ECPR are complex.[5] In order to inform the update of international guidelines[6, 7], we therefore plan to perform a systematic review of the literature.

Objectives (PICO question)

Population: Adults (≥ 18 years) and children (<18 years) with cardiac arrest in any setting (out-of-hospital or in-hospital)

Interventions: ECPR, including extracorporeal membrane oxygenation or cardiopulmonary bypass, during cardiac arrest

Control: Manual CPR and/or mechanical CPR

Outcomes: Clinical outcomes, including, but not necessarily limited to, return of spontaneous circulation, survival/survival with a favorable neurological outcome at hospital discharge/30 days, and survival/survival with a favorable neurological outcome after hospital discharge/30 days (e.g. 90 days, 180 days, 1 year). The final included outcomes will depend on the available data and subsequent outcome prioritization by the ILCOR task forces. This might include organ donation as an outcome if data is available.

Definitions

There have been multiple definitions of ECPR. For this review, we will use the following definition which is generally consistent with ongoing updates to the ECPR definition by the Extracorporeal Life Support Organization (ELSO)[8]:

ECPR is the application of rapid-deployment venoarterial extracorporeal membrane oxygenation to provide circulatory support in patients in whom conventional cardiopulmonary resuscitation (CPR) is unsuccessful in achieving sustained return of spontaneous circulation (sustained ROSC). Sustained ROSC is deemed to have occurred when chest compressions are not required for 20 consecutive minutes and signs of circulation persist.

We recognize that individual studies might have used different definitions and whether or not individual studies are eligible for inclusion will be determined on a case-by-case basis. However, studies exclusively assessing use of extracorporeal life support for cardiac and/or respiratory failure after sustained return of spontaneous circulation will not be included. Studies assessing extracorporeal circulation for deep hypothermia (or other conditions) will only be included if cardiac arrest is documented.

METHODS

Eligibility criteria

Randomized trials, non-randomized controlled trials, and observational studies (cohort studies and case-control studies) with a control group (i.e. patients not receiving ECPR) will be included. Animal studies, ecological studies, case series, case reports, reviews, abstracts, editorials, comments, and letters to the editor will not be included. There will be no limitations on publication period or study language. The population includes patients suffering from IHCA or OHCA of any origin, without age restriction. Studies with ≤ 5 patients receiving ECPR or studies with no timing on ECPR will be excluded. Studies assessing cost-effectiveness of ECPR will be included for a descriptive summary.

Information sources

We will search the following electronic bibliographic databases: MEDLINE, EMBASE, and Evidence-Based Medicine Reviews (which includes the Cochrane Library). The bibliographies of included articles will be reviewed for potential additional articles. To identify potential ongoing trials, we will search the International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/).

Search strategy

MEDLINE

1 Extracorporeal Circulation/

2 Cardiopulmonary Bypass/

3 Extracorporeal Membrane Oxygenation/

4 Heart Bypass, Left/

5 extracorporeal circulation*.tw,kf.

6 extra-corporeal circulation*.tw,kf.

7 extracorporeal blood flow*.tw,kf.

8 extra-corporeal blood flow*.tw,kf.

9 extracorporeal bypass*.tw,kf.

10 extra-corporeal bypass*.tw,kf.

11 extracorporeal perfusion*.tw,kf.

12 extra-corporeal perfusion*.tw,kf.

13 (artificial adj2 circulation*).tw,kf.

14 (cardiac adj2 bypass*).tw,kf.

15 (heart adj1 bypass*).tw,kf.

16 extracorporeal cardiopulmonary resuscitation*.tw,kf.

17 extra-corporeal cardiopulmonary resuscitation*.tw,kf.

18 extracorporeal CPR.tw,kf.

19 extra-corporeal CPR.tw,kf.

20 ECPR.tw,kf.

21 E-CPR.tw,kf.

22 cardiopulmonary bypass*.tw,kf.

23 CPB.tw,kf.

24 heart-lung bypass*.tw,kf.

25 (extracorporeal adj3 oxygenation*).tw,kf.

26 (extra-corporeal adj3 oxygenation*).tw,kf.

27 ECMO.tw,kf.

28 extrapulmonary oxygenation*.tw,kf.

29 extra-pulmonary oxygenation*.tw,kf.

30 extracorporeal life support*.tw,kf.

31 extra-corporeal life support*.tw,kf.

32 ECLS.tw,kf.

33 left ventric* bypass*.tw,kf. (198)

34 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 18 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33

35 exp Heart Arrest/

36 Ventricular Fibrillation/

37 Tachycardia, Ventricular/

38 heart arrest*.tw,kf.

39 cardiac arrest*.tw,kf.

40 circulat* arrest*.tw,kf.

41 heart standstill*.tw,kf.

42 cardiopulmonary arrest*.tw,kf.

43 cardiovascular arrest*.tw,kf.

44 asystol*.mp.

45 ventric* fibrillation*.tw,kf.

46 ventric* tachy*.tw,kf.

47 ventricular tachyarrhythmia*.tw,kf.

48 pulseless electrical activity.mp.

49 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48

50 34 and 49

51 exp Animals/ not Humans/

52 50 not 51

53 limit 52 to (case reports or comment or editorial or letter)

54 52 not 53

EMBASE

1 extracorporeal circulation/

2 cardiopulmonary bypass/

3 extracorporeal oxygenation/

4 heart left ventricle bypass/

5 extracorporeal circulation*.tw,kw.

6 extra-corporeal circulation*.tw,kw.

7 extracorporeal blood flow*.tw,kw.

8 extra-corporeal blood flow*.tw,kw.

9 extracorporeal bypass*.tw,kw.

10 extra-corporeal bypass*.tw,kw.

11 extracorporeal perfusion*.tw,kw.

12 extra-corporeal perfusion*.tw,kw.

13 (artificial adj2 circulation*).tw,kw.

14 (cardiac adj2 bypass*).tw,kw.

15 (heart adj1 bypass*).tw,kw.

16 extracorporeal cardiopulmonary resuscitation*.tw,kw.

17 extra-corporeal cardiopulmonary resuscitation*.tw,kw.

18 extracorporeal CPR.tw,kw.

19 extra-corporeal CPR.tw,kw.

20 ECPR.tw,kw.

21 E-CPR.tw,kw.

22 cardiopulmonary bypass*.tw,kw.

23 CPB.tw,kw.

24 heart-lung bypass*.tw,kw.

25 (extracorporeal adj3 oxygenation*).tw,kw.

26 (extra-corporeal adj3 oxygenation*).tw,kw.

27 ECMO.tw,kw.

28 extrapulmonary oxygenation*.tw,kw.

29 extra-pulmonary oxygenation*.tw,kw.

30 extracorporeal life support*.tw,kw.

31 extra-corporeal life support*.tw,kw.

32 ECLS.tw,kw.

33 left ventric* bypass*.tw,kw.

34 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33

35 heart arrest/

36 cardiopulmonary arrest/

37 heart ventricle fibrillation/

38 heart ventricle tachycardia/

39 heart arrest*.tw,kw.

40 cardiac arrest*.tw,kw.

41 circulat* arrest*.tw,kw.

42 heart standstill*.tw,kw.

43 cardiopulmonary arrest*.tw,kw.

44 cardiovascular arrest*.tw,kw.

45 asystol*.mp.

46 ventric* fibrillation*.tw,kw.

47 ventric* tachy*.tw,kw.

48 ventricular tachyarrhythmia*.tw,kw.

49 pulseless electrical activity.mp.

50 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49

51 34 and 50

52 (exp animal/ or nonhuman/) not exp human/

53 51 not 52

54 limit 53 to (editorial or letter or reports)

55 53 not 54

56 limit 55 to embase

Evidence-Based Medicine Reviews

1 Extracorporeal Circulation/

2 Cardiopulmonary Bypass/

3 Extracorporeal Membrane Oxygenation/

4 Heart Bypass, Left/

5 extracorporeal circulation*.ti,ab,kf.

6 extra-corporeal circulation*.ti,ab,kf.

7 extracorporeal blood flow*.ti,ab,kf.

8 extra-corporeal blood flow*.ti,ab,kf.

9 extracorporeal bypass*.ti,ab,kf.

10 extra-corporeal bypass*.ti,ab,kf.

11 extracorporeal perfusion*.ti,ab,kf.

12 extra-corporeal perfusion*.ti,ab,kf.

13 (artificial adj2 circulation*).ti,ab,kf.

14 (cardiac adj2 bypass*).ti,ab,kf.

15 (heart adj1 bypass*).ti,ab,kf.

16 extracorporeal cardiopulmonary resuscitation*.ti,ab,kf.

17 extra-corporeal cardiopulmonary resuscitation*.ti,ab,kf.

18 extracorporeal CPR.ti,ab,kf.

19 extra-corporeal CPR.ti,ab,kf.

20 ECPR.ti,ab,kf.

21 E-CPR.ti,ab,kf.

22 cardiopulmonary bypass*.ti,ab,kf.

23 CPB.ti,ab,kf.

24 heart-lung bypass*.ti,ab,kf.

25 (extracorporeal adj3 oxygenation*).ti,ab,kf.

26 (extra-corporeal adj3 oxygenation*).ti,ab,kf.

27 ECMO.ti,ab,kf.

28 extrapulmonary oxygenation*.ti,ab,kf.

29 extra-pulmonary oxygenation*.ti,ab,kf.

30 extracorporeal life support*.ti,ab,kf.

31 extra-corporeal life support*.ti,ab,kf.

32 ECLS.ti,ab,kf.

33 left ventric* bypass*.ti,ab,kf.

34 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 18 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33

35 exp Heart Arrest/

36 Ventricular Fibrillation/

37 Tachycardia, Ventricular/

38 heart arrest*.ti,ab,kf.

39 cardiac arrest*.ti,ab,kf.

40 circulat* arrest*.ti,ab,kf.

41 heart standstill*.ti,ab,kf.

42 cardiopulmonary arrest*.ti,ab,kf.

43 cardiovascular arrest*.ti,ab,kf.

44 asystol*.mp.

45 ventric* fibrillation*.ti,ab,kf.

46 ventric* tachy*.ti,ab,kf.

47 ventricular tachyarrhythmia*.ti,ab,kf.

48 pulseless electrical activity.mp.

49 35 or 36 or 37 o 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48

50 34 and 49

Data management

RevMan (The Cochrane Collaboration, 2014) will be used to perform meta-analysis of the study data. GRADEpro (McMaster University, 2014) will be used for drafting of the GRADE tables. SAS software, version 9.4 (SAS Institute, Cary, NC, USA) will be used for meta-regression if pertinent.

Selection process

Two reviewers, using pre-defined screening criteria, will independently screen all titles and abstracts retrieved from the systematic review. The reviewers will be blinded to authors and journal titles during this screening stage. Any disagreement regarding inclusion or exclusion will be resolved via discussion between the reviewers and with a third reviewer if needed. The Kappa-value for inter-observer variance will be calculated. In case of only weak or moderate agreement between reviewers (i.e. a Kappa < 0.80[9]) a third reviewer will review all excluded titles and abstracts to ensure optimized sensitivity. Two reviewers will then review the full text-reports of all potentially relevant publications passing the first level of screening. Any disagreement regarding eligibility will be resolved via discussion and study authors will be contacted if pertinent. The final report will include a Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) diagram showing the number of studies remaining after each stage of the selection process. This will include reasons for exclusion of full text articles.

Data collection process

Two reviewers using a pre-defined standardized data extraction form will extract data as pertinent to the PICO. Any missing statistical parameters (e.g. relative risk, odds ratio) of importance and variance measures (e.g. confidence intervals) will be calculated if data permits. Any discrepancy regarding the extracted data will be identified and resolved via discussion.

Data items

The following data will be extracted as relevant:

- General Information
    - First author name
    - Year of publication
    - Geographical location of the study (country, continent)
    - Study design
    - Inclusion and exclusion criteria
    - Years of patient enrollment

        - Number of patients screened and analyzed
        - Precise intervention/exposure/comparator
        - Duration of follow-up
    - Participants
        - Summary demographics
            - Age (mean/median)
            - Gender (proportion of females)
            - Race (proportion of white, black, Asian, other)
        - Age category (pediatric, adult, combined)
        - Location of the cardiac arrest (IHCA vs. OHCA)
        - Shockable/non-shockable rhythms
        - Etiology of the cardiac arrest (presumed cardiac vs. non-cardiac)
        - Bystander CPR (for OHCA studies)
        - Witnessed status (for OHCA studies)
        - Targeted temperature management
        - Anatomical location of cannulation
        - Coronary angiography
    - Primary/secondary outcomes
    - Relevant results

Outcomes

Based on review of the included studies according to version 1 of the protocol, the ILCOR task forces decided to include the following outcomes:

- Survival at discharge/1 month (discharge, 28 days, 30 days, and 1 month combined)
- Long-term survival (3 months, 6 months, 1 year, 2 years and "long term" combined)
- Survival analysis (i.e. results reported as hazard ratios irrespective of the length of follow-up)
- Neurological outcome at discharge/1 month (discharge, 30 days and 1 month combined)
- Long-term neurological outcome (3 months, 6 months, 1 year, 2 years and "long term" combined)

Return of spontaneous circulation was not included as an outcome since it is difficult to define in this patient population and variably defined.

Risk of bias in individual studies

Two investigators will independently assess risk of bias for the included studies. Risk of bias will be assessed by use of the Cochrane risk-of-bias tool[10] for controlled trials and the ROBINS-I tool[11] for observational studies. The Cochrane risk-of-bias tool involves assessment of the risk of bias from each of six domains including (1) generation of a random allocation sequence, (2) concealment of the allocation sequence, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, and (6) selective reporting. Other items that do not necessarily impact bias may also be assessed such as industry sponsorship, single trial centers, and improper analyses or potential fabrication of study data.[10]

In the ROBINS-I tool, risk of bias is assessed within specified domains, including (1) bias due to confounding, (2) bias in selection of participants into the study, (3) bias in classification of interventions, (4) bias due to deviations from intended interventions (5) bias due to missing data, (6) bias in measurement of outcomes, (7) bias in selection of the reported result, and (8) overall bias.[11] Bias assessments will be tabulated with detailed explanations when studies are downgraded.

Heterogeneity, data synthesis and meta-regression

All data will be synthesized in accordance with the PRISMA guidelines. Studies will be assessed for clinical (i.e. participants, interventions, and outcomes), methodological (i.e. study design or risk of bias) and statistical heterogeneity.[10] Statistical heterogeneity will be assessed using forest plots, Chi-squared statistics, and I-squared statistics. A p-value of < 0.10 or I-squared statistic of $>50\%$ will indicate substantial statistical heterogeneity, and in such cases random-effects meta-analyses will be performed.[10] In the case of homogeneity, a fixed-effects model will be used. A narrative synthesis will be conducted if heterogeneity (i.e. clinical, methodological, and statistical) is deemed too substantial across studies to allow for meaningful meta-analyses.

If feasible, meta-analyses will be conducted separately for the following groups: 1) adult IHCA, 2) adult OHCA, 3) pediatric IHCA, and 4) pediatric OHCA. If the data permits additional subgroup analyses, these will be performed and could include subgroups based on 1) the etiology of the cardiac arrest (cardiac vs. non-cardiac), 2) prehospital vs. inhospital initiation of ECPR for OHCA, and 3) shockable vs. non-shockable initial rhythm. Subgroup analyses will be performed per study type (i.e. randomized trials vs. observational studies).

In case of overlap in data between studies included in the meta-analyses, the risk of bias within the individual studies will be compared and the study with the least risk of bias will be included. If the risk of bias is similar, we will include the study with the largest sample size. Consistent with the I-ROBINS recommendations, observational studies with a critical risk of bias will not be included in meta-analyses.[11]

Given that most studies will be observational with results reported as adjusted odds ratios, the "generic inverse variance method" in RevMan will be used for meta-analyses.[10] There will be no attempt to account for missing data within included studies.

In the case of heterogeneity within the above groups, meta-regression will be conducted to identify potential statistically significant determinants of heterogeneity in the pooled effect estimates at an alpha level of 0.05. The following variables are specified *a priori* for inclusion in the univariate model: Study design (i.e. randomized vs. observational), sample size (in quartiles), continent of conduct (North America, Europe, Asia, other), year (median) of patient enrollment, participant age (median), and initial cardiac rhythm (proportion of shockable rhythms). Other variables might be included based on the results of the systematic review. If there is a sufficient ratio of studies to co-variates, each co-variate will be entered in a multivariate meta-regression model using a backward elimination approach at a p-value > 0.05. If this is not the case, only bivariable assessments will be made. Meta-regression will only be performed if the number of studies is ≥ 10.[10]

Publication bias will be evaluated using funnel plots, the Egger test, the Begg test, and the Harbord test as appropriate, depending on the degree of heterogeneity observed.[10] However, these statistical tests will only be conducted if the number of studies is ≥ 10.[10]

Number needed to treat (NNT) will be calculated based on the pooled odds ratios and various estimates of baseline risk.[12, 13]

Confidence in cumulative evidence

The quality of the overall evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology ranging from very low quality of evidence to high quality of evidence.[14] Detailed assessment of overall risk of bias, inconsistency, indirectness, imprecision and potential other issues such as publication bias will be tabulated using the GRADEpro software (McMaster University, 2014).

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