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Review

Epinephrine for out of hospital cardiac arrest: A systematic review and meta-analysis of randomized controlled trials☆

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Abstract

Objective: To evaluate the effectiveness of epinephrine, compared with control treatments, on survival at admission, ROSC, survival to discharge, and a favorable neurologic outcome in adult patients during OHCA.

Data source: MEDLINE and PubMed from inception to August 2018.

Study selection: Randomized controlled trials (RCTs) on adult patients after out-of-hospital cardiac arrest (OHCA) treated with epinephrine versus controls.

Data extraction: Independent, double-data extraction; risk of bias assessment with Cochrane Collaboration's criteria.

Data synthesis: 15 RCTs representing 20,716 OHCA adult patients. When epinephrine was compared with a placebo/no drugs, survival to hospital discharge (RR: 1.34, 95% CI: 1.08−1.67), ROSC (RR: 2.03, 95% CI: 1.18−3.51) and survival to hospital admission (RR: 2.04, 95% CI: 1.22−3.43) were increased, but favorable neurologic outcome was not significantly different (RR: 1.22, 95% CI: 0.99−1.51). Patients treated with the high-dose epinephrine (HDE) had a higher rate of ROSC (standard-dose epinephrine (SDE) versus HDE, RR: 0.85, 95% CI: 0.74−0.97, p = 0.01) and increased survival to hospital admission (SDE versus HDE, RR: 0.86, 95% CI: 0.75−0.99, p = 0.04) compared with those treated with SDE. No considered treatments improved the neurological outcome after OHCA.

Conclusions: In OHCA, standard or high doses of epinephrine should be used because they improved survival to hospital discharge. There was also a clear advantage of using epinephrine over a placebo or no drugs in the considered outcomes.

Keywords: Out-of-hospital cardiac arrest, Epinephrine, Hospital survival, Fragility index

Introduction

Overall survival to hospital discharge after out-of-hospital cardiac arrest (OHCA) ranges from 8% to 10%.[1] Several factors affect hospital survival, such as cardiopulmonary resuscitation quality and post-resuscitation care. Standardized algorithms for advanced life support (ALS) and post-resuscitation care are included in the European guidelines for resuscitation.[2] The current ALS guidelines recommend giving epinephrine (1 mg) every 3−5 min until return of spontaneous circulation (ROSC) is achieved. The optimal dose of epinephrine is not known, and there are no human data supporting the use of repeated doses. Increasing cumulative doses of epinephrine during resuscitation of patients with asystole and PEA are an independent risk factor for an unfavorable functional outcome and in-hospital mortality.[2] According to previous systematic reviews, the use of adrenaline for OHCA increased the rates of ROSC but did not improve long-term survival or favourable neurological outcome.[2] Recently, the

☆ The authors received no financial support for this study.

DOI of original article: http://dx.doi.org/10.1016/j.resuscitation.2019.01.016

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http://dx.doi.org/10.1016/j.resuscitation.2019.10.026

PARAMEDIC2 trial showed that epinephrine in OHCA was associated with a slight improvement in the 30-day survival[3]; although there were more survivors with a favourable neurological outcome in the epinephrine group, this was not statistically significant, and there were also more survivors in the epinephrine group with severe neurologic impairment.[3]

The aim of this systematic review and meta-analysis was to evaluate the effectiveness of epinephrine, compared with control treatments, on survival at admission, ROSC, survival at discharge, and favourable neurological outcome in adult patients during OHCA. As studies include different control treatments during OHCA, we planned (a priori) sub group analyses according to (1) the treatments used in the control groups (placebo/no drugs, high dose of epinephrine and epinephrine plus vasopressin) and (2) the fragility index, which was calculated for the primary outcome for each study.

Methods

This meta-analysis is registered with PROSPERO (number CRD42018114339).

Data sources and search strategy

We aimed to identify all randomized controlled trials (RCTs) on adult patients after OHCA who were treated with epinephrine versus a control. The electronic search strategy was applied with standard filters for identification of RCTs. The databases searched were MEDLINE and PubMed (from inception to August 2018). We applied an English language restriction. The search strategy included the following keywords: *cardiac arrest, out-of-hospital cardiac arrest, circulatory arrest, cardiopulmonary resuscitation, adrenaline, epinephrine, vasopressin, mortality to hospital admission, survival to hospital admission, humans and randomized clinical trial.*

Study selection

We included only published full papers. When more than one RCT was not available for each topic, we considered observational clinical studies. Data were independently extracted from each study by two authors (MV and PB) using a data recording form developed for this purpose.

Interventions

The interventions of interest were the comparisons between standard dose epinephrine (SDE) versus a placebo or no drugs, SDE versus high dose epinephrine (HDE) >1 mg per dose, and SDE versus epinephrine + vasopressin.

Outcome

The primary outcome was survival to hospital discharge after OHCA. The secondary outcomes were return of spontaneous circulation (ROSC), survival to hospital admission, and a good neurological outcome at discharge. A good neurological outcome was defined as a cerebral performance category (CPC) of 1 and 2, an overall performance category (OPC) of 1 and 2, a Modified Rankin Scale (mRS) score ≤ 3, and a normal or moderate disability at hospital discharge.

Data extraction and quality assessment

The initial data selection was performed by screening titles and abstracts by two pairs of independent reviewers (MV and PB; GS and CI). The full-text copy of potential relevant studies was obtained for detailed evaluation. Data from each study were independently extracted by two pairs of independent reviewers (MV and PB; GS and CI) using a pre-standardized data abstraction form. Data extracted from the studies were independently checked for accuracy by two reviewers (MV and GS). A quality assessment was conducted by two reviewers (CI and PB) with the GRADE approach. The quality evaluation included (1) the use of randomization sequence generation, (2) the reporting of allocation concealment, (3) blinding, (4) reporting incomplete outcome data, and (5) comparability of the groups at the baseline. We solved any possible disagreement by consensus through consultation with an external reviewer, if needed. We further calculated the fragility index (FI) for each study to assess its robustness. The FI was calculated on the variable/s that each study declared as a primary outcome/s.

Quantitative analysis

This meta-analysis was conducted according to PRISMA guidelines.[4] A mixed random effect with the DerSimonian and Laird method was used in this meta-analysis. The results were graphically represented with forest plot graphs. The Relative Risk (RR) and 95% CI for each outcome were separately calculated for each trial with grouped data using the intention-to-treat principle. The choice to use RR was driven by the design of the meta-analysis based on the RCTs. Tau^2 defined the variance between the studies. The difference in estimates of the treatment effect between the treatment and control groups for each hypothesis was tested using a two-sided z test with statistical significance considered at a p value of less than 0.05. The homogeneity assumption was checked by a Q test with a degree of freedom (df) equal to the number of analyzed studies minus 1. The heterogeneity was measured by I, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance. I^2 was calculated from basic results obtained from a typical meta-analysis as $I^2 = 100\%\ A \sim (Q - \_df)/Q$, where Q is Cochran's heterogeneity statistic and df is the degree of freedom. A value of 0% indicates no observed heterogeneity, and larger values demonstrate increasing heterogeneity.

We planned (a priori) to do subgroup analyses to analyze all the outcomes according to the following categories when possible: standard-dose epinephrine (SDE) versus a placebo/no drugs, SDE versus high-dose epinephrine (HDE), and SDE versus epinephrine + vasopressin (Epi + Vaso).

We evaluated the FI of the RCTs included in this meta-analysis using a two-by-two contingency table and a p value produced by the Fisher exact test.[5] According to the FI, we defined robust RCTs with $FI > 0$, and not robust RCTs with $FI = 0$. We further analyzed all outcomes according to (1) robust RCTs with $FI > 0$, and (2) not robust RCTs with $FI = 0$. The analyses were conducted with OpenMetaAnalyst (version 6) and SPSS version 20 (IBM SPSS).

To evaluate potential publication bias, a weighted linear regression was used, with the natural log of the OR as the dependent variable, and the inverse of the total sample size as the independent variable. This is a modified Macaskill's test that gives more balanced type-I error rates in the tail probability areas in comparison to other publication bias tests.[6]

Results

Study selection

A total of 1986 studies were identified of which 783 were duplicates; 108 full-text articles were assessed for eligibility; and 15 RCTs with 20,716 patients were included in the final analysis.[7–20] Fig. 1 shows the flow diagram for included studies.

Characteristics of the included studies

Patients with OHCA were randomized to receive SDE versus a placebo/no drugs in three studies.[3,7,8] Six studies compared patients receiving SDE versus HDE randomly,[9–14] whereas six studies compared SDE versus Epi + Vaso.[15–20] Five studies considered more than one primary outcome.[10,13–15,17]. According to the FI, only three studies had an FI > 0.[8,10,14] The characteristics of the included studies are reported in Supplementary Table 1.

Quality assessment

All the included RCTs had a low risk of bias. The Table 2 Supplementary materials showed the quality assessment for each included study.

Primary outcome

SDE improved survival to hospital discharge compared with placebo/no drugs (SDE versus placebo/no drugs, RR: 1.34, 95% CI: 1.08–1.67, p = 0.00). Fig. 2 shows the forest plot comparing SDE vs placebo/no drugs for the survival to hospital discharge. This result was confirmed by analyzing robust and not-robust trials (SDE FI > 0 versus control, RR: 1.32, 95% CI: 1.06–1.65, p = 0.01; SDE FI = 0 versus control, RR: 1.05, 95% CI: 0.86–1.28, p = 0.63).

There was no difference in survival to hospital discharge when comparing SDE with HDE (SDE versus HDE, RR: 1.03, 95% CI: 0.75–1.41, p = 0.80) and SDE with Epi + Vaso (SDE versus Epi + Vaso, RR: 0.99, 95% CI: 0.69–1.43, p = 0.99) (Supplementary material).

Secondary outcomes

SDE improved ROSC when compared with placebo/no drugs (SDE versus a placebo/no drugs, RR: 2.03, 95% CI: 1.18–3.51, p = 0.01). Patients treated with the HDE had a higher rate of ROSC compared with those treated with the SDE (SDE versus HDE, RR: 0.85, 95% CI: 0.74–0.97, p = 0.01). Fig. 3 shows the forest plot for ROSC comparing SDE versus placebo/no drugs (Fig. 3A), and HDE (Fig. 3B).

There was no difference in the rate of ROSC between the SDE and the Epi + Vaso (SDE versus Epi + Vaso, RR: 1.02, 95% CI: 0.91–1.14, p = 0.71) (Supplementary material). There was no difference in the

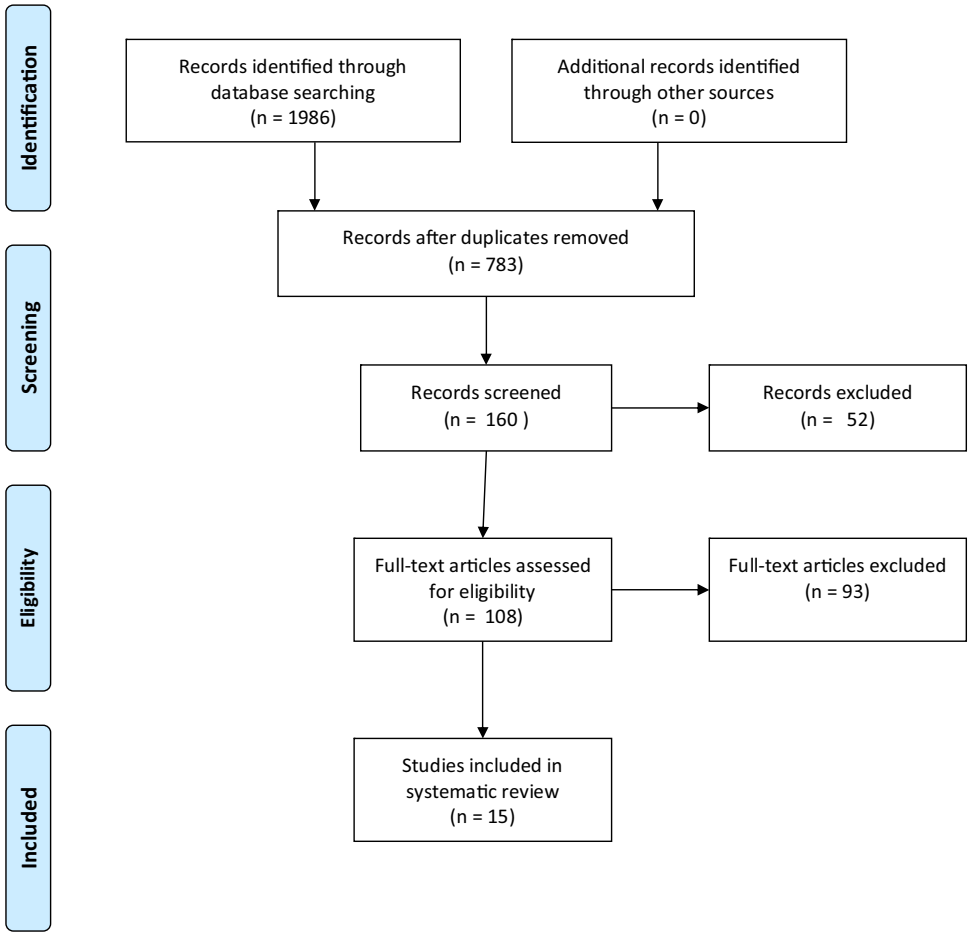

Fig. 1 – PRISMA flow diagram of included studies.

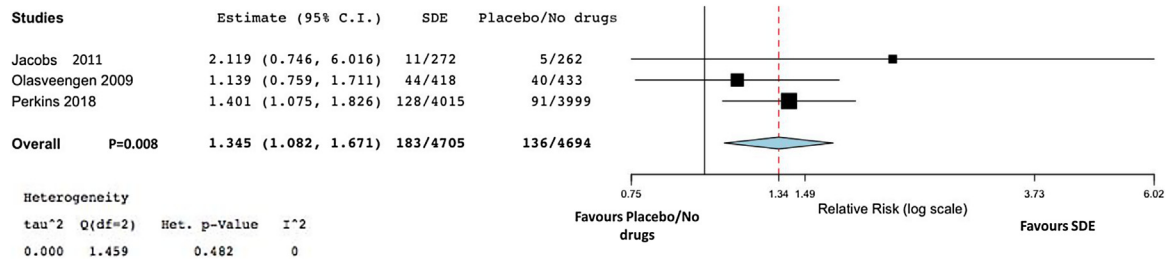

Fig. 2 – Forest plot for survival to the hospital discharge comparing SDE versus Placebo/No drugs. Weights: Jacobs: 4.334%, Olasveengen: 28.550%, Perkins: 67.116%. Values were presented as relative risk and 95% CI. SDE: standard dose epinephrine.

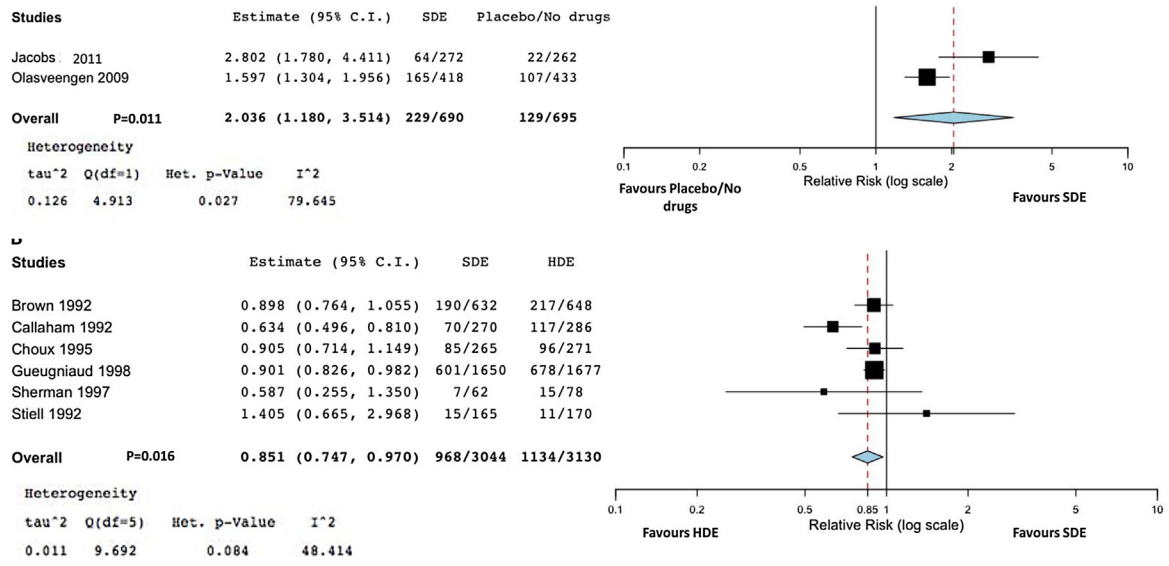

Fig. 3 – Panel A: forest plot for ROSC comparing SDE versus Placebo/NO drugs. Weights: Jacobs: 43.212%, Olasveengen: 56.788%.
Panel B: forest plot for ROSC comparing SDE versus HDE. Weights: Brown: 25.433%, Callaham: 16.828%, Choux: 17.435%, Gueugniaud: 35.164%, Sherman: 2.312%, Stiell: 2.829%. Values were presented as relative risk and 95% CI. SDE: standard dose epinephrine, HDE: high dose epinephrine.

ROSC, even in the analysis including the robust and the not-robust RCTs (SDE FI > 0 versus control, RR: 1.21, 95% CI: 0.46–3.20, p = 0.69; SDE FI = 0 versus control, RR: 1.10, 95% CI: 0.93–1.29, p = 0.23) (Supplementary material).

SDE improved survival to hospital admission when compared with a placebo/no drugs (SDE versus a placebo/no drugs, RR: 2.04, 95% CI: 1.22–3.43, p = 0.00). Patients treated with the HDE had a better survival to hospital admission than those treated with the SDE (SDE versus HDE, RR: 0.86, 95% CI: 0.75–0.99, p = 0.04). Fig. 4 shows the forest plot for survival to hospital admission comparing SDE vs placebo/no drugs (Fig. 4A), and HDE (Fig. 4B).

There was no difference in survival to hospital admission when comparing SDE with the Epi + Vaso (SDE versus Epi + Vaso, RR: 0.87, 95% CI: 0.74–1.01, p = 0.07) (Supplementary material).

There was no difference in patients discharged with a favorable neurologic outcome when comparing SDE with a placebo/no drugs (SDE versus a placebo/no drugs, RR: 1.21, 95% CI: 0.94–1.54, p = 0.12) (Fig. 5A), when comparing SDE with HDE (SDE versus HDE, RR: 1.20, 95% CI: 0.73–1.95, p = 0.45) (Fig. 5B), when comparing SDE with Epi + Vaso (SDE versus Epi + Vaso, RR: 1.35, 95% CI: 0.91–2.00, p = 0.13), and in robust trials (SDE FI > 0 versus control, RR: 1.18, 95% CI: 0.91–1.53, p = 0.21) (Supplementary material).

Discussion

In this systematic review and meta-analysis including 20,716 patients treated with epinephrine during OHCA, we found that (1) the rate of survival to hospital discharge, ROSC, and survival to hospital admission was higher with epinephrine in comparison with a placebo/no drugs; (2) there were no differences in the considered outcomes between epinephrine and epinephrine plus vasopressin; (3) in comparison with SDE, HDE increased the rate of ROSC and survival to hospital admission but did not increase survival to hospital discharge or good neurological outcome; and (4) considering the robust RCTs, epinephrine increased short (ROSC/survival to hospital admission) and longer-term survival (survival to discharge) but did not improve the secondary outcomes (neurological outcome at discharge).

To our knowledge, this is the first meta-analysis that (1) compares epinephrine with a placebo/no drugs; (2) stratifies the RCTs according

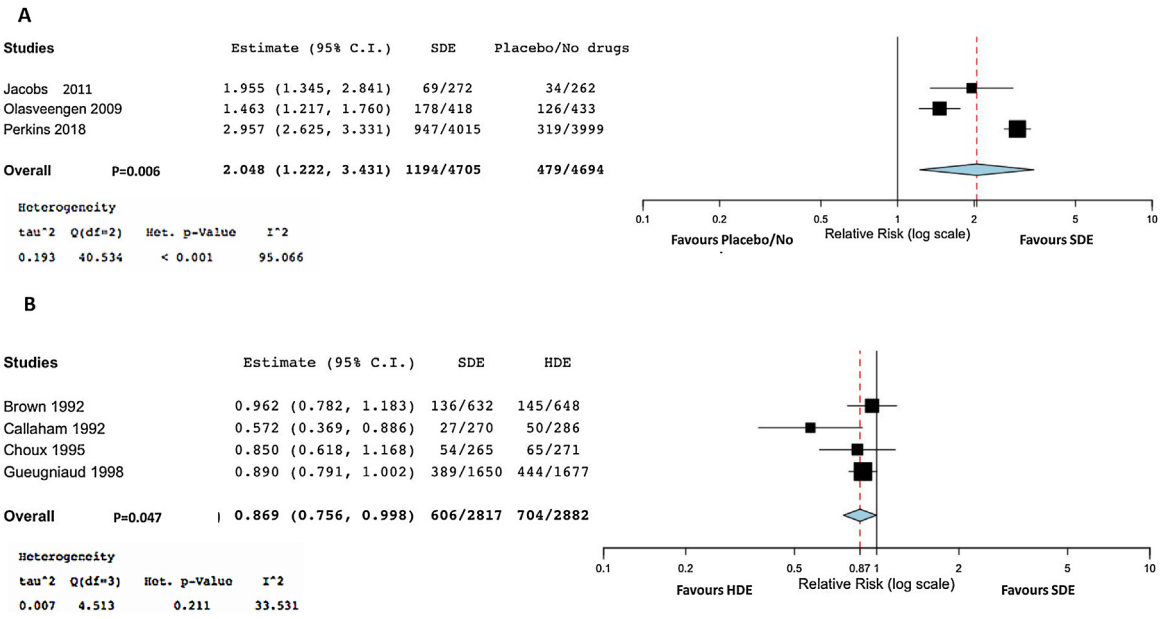

Fig. 4 – Panel A: forest plot for survival to the hospital admission comparing SDE versus Placebo/NO drugs. Weights: Jacobs: 30.271%, Olasveengen: 34.412%, Perkins: 35.317%.
Panel B: forest plot for survival to the hospital admission comparing SDE versus HDE. Weights: Brown: 27.985%, Callaham: 8.876%, Choux: 15.113%, Gueugniaud: 48.025%. Values were presented as relative risk and 95% CI. SDE: standard dose epinephrine, HDE: high dose epinephrine.

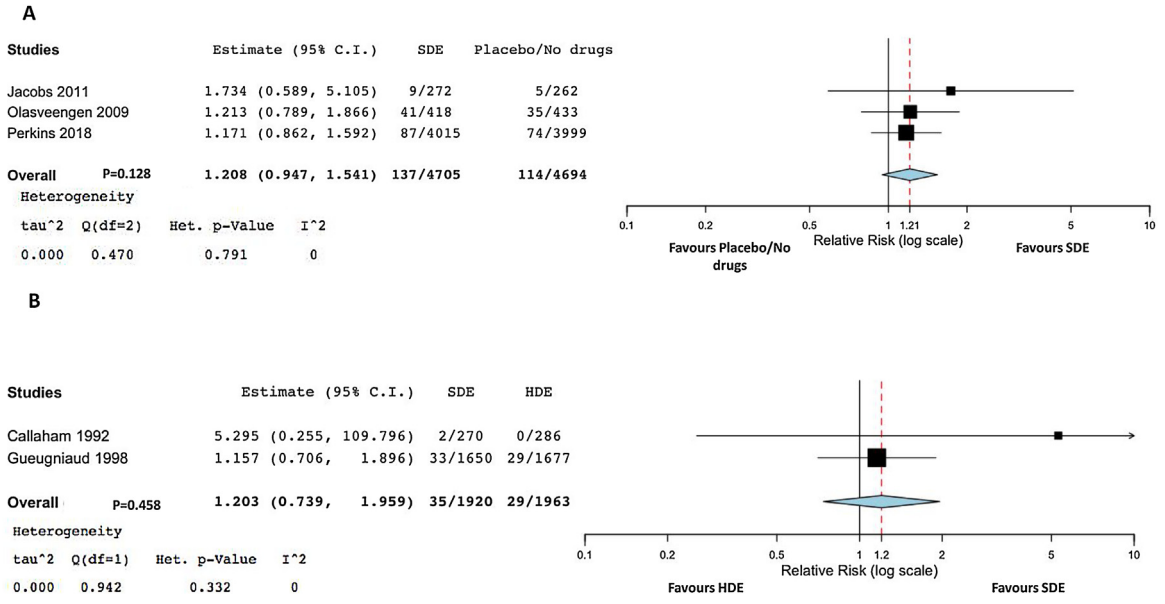

Fig. 5 – Panel A: forest plot for favorable neurologic outcome comparing SDE versus Placebo/NO drugs. Weights: Jacobs: 5.081%, Olasveengen: 31.969%, Perkins: 62.950%.
Panel B: forest plot for favorable neurologic outcome comparing SDE versus HDE. Weights: Callaham: 2.588%, Gueugniaud: 97.412%. Values were presented as relative risk and 95% CI. SDE: standard dose epinephrine, HDE: high dose epinephrine.

to the FI; and (3) includes the study by Perkins et al. [3] Recently, Zhang et al. performed a systematic review and meta-analysis comparing epinephrine with epinephrine plus vasopressin and including Asian, American, and European studies.[21] Interestingly, Zhang et al. found that epinephrine improved ROSC only in Asian patients, and not in European and American patients.[21] However, the Asian RCTs were of very poor quality, and the meta-analysis had a large heterogeneity.[21]

Lin et al. performed a subgroup analysis of the RR comparing epinephrine with HDE, and epinephrine with epinephrine plus vasopressin.[22] This meta-analysis did not include the study by

Perkins et al. [3] and did not include a meta-analysis comparing epinephrine and a placebo/no drugs.[22] Two previous meta-analyses, including RCTs and observational studies, found that epinephrine did not increase survival to hospital discharge.[23,24] Our results were very different from the previous reviews,[22–24] because we found a better survival to hospital discharge in OHCA.

Previous studies report that epinephrine is associated with a significant improvement in ROSC and survival to hospital admission, but makes no difference to survival to hospital discharge and favorable neurologic outcome.[25] Even the recent study by Perkins et al. (PARAMEDIC-2),[3] showed that epinephrine, when compared with a placebo, had a powerful effect on ROSC after OHCA, but made only a small absolute increase in survival and made no improvement in a favorable functional recovery.

Our review suggests epinephrine, when compared with a placebo/no drugs, improves short-term and longer-term outcomes. These results should encourage further studies evaluating the real benefit of epinephrine on short-term and long-term outcomes, even if successful long-term outcomes are also impacted by in-hospital management interventions that occur for several days after OHCA.[26] For example, optimizing respiratory and cardiac function after cardiac arrest may improve long-term outcomes beyond the use of epinephrine during OHCA.[27]

Current guidelines on cardiac arrest state that it is reasonable to consider administering 1 mg of epinephrine every 3–5 min during adult cardiac arrest.[2] In the present meta-analysis, a high dose of epinephrine, when compared with a standard dose of epinephrine, had a better rate of ROSC and survival to hospital admission, but a similar effect on survival to hospital discharge and a good neurologic outcome. A high dose of epinephrine may increase coronary perfusion pressure and peripheral vasoconstriction.[2] However, a high dose of epinephrine may also have detrimental effects, such as an increase in myocardial oxygen consumption, ectopic ventricular arrhythmias, transient hypoxemia from pulmonary arteriovenous shunting, impaired microcirculation, and worse post–cardiac arrest myocardial dysfunction.[25]

Recently, the concept of fragility index (FI) was introduced with the purpose of measuring the robustness of RCTs from a statistical point of view.[28,29] According to the current definition, RCTs with a larger FI have more robust findings when compared with the studies with a low FI.[29] The FI has not been assessed in previous meta-analyses of epinephrine.[30] As a low FI reinforces the finding that the robustness of evidence available to clinical decision makers is limited, we measured the FI for all the included RCTs. Although all the included RCTs had a low risk of bias, only three RCTs showed an FI of more than 0. In terms of hospital discharge and survival to hospital admission, we found similar results between the subgroup analysis of the RCTs with an FI >0 and the pooled group. The assessment of FI has added robustness to the results of our meta-analysis and should, in our view, be considered in future meta-analyses. In line with previous systematic reviews,[22] we also employed the Cochrane Collaboration tool and the GRADE criteria to assess the risk of bias for our included studies.

Limitations

This systematic review and meta-analysis has limitations that need to be addressed. First, we evaluated treatments based on guidelines for cardiac arrest that are not universally accepted.[2] Second, we found heterogeneity >25% in 10 out of 20 comparisons for the considered outcomes. Third, the results of the FI should be interpreted with caution. Fourth, we included RCTs and excluded prospective and retrospective studies. Lastly, the Olasveengen 2009 study was not a comparison of SDE versus placebo; it compared intravenous (IV) cannulation and drug administration with no IV cannulation or drugs, 79% of patients in the IV group were treated with epinephrine.[8]

Conclusions

In OHCA, standard or high doses of epinephrine should be used, because they improved survival to hospital discharge. There was also a clear advantage of using epinephrine over a placebo or no drugs in the considered outcomes. Further trials are needed to assess the optimal dose of epinephrine for OHCA, because this remains unknown. High dose epinephrine (HDE) was associated with better ROSC and survival to hospital admission; we suggest that use of HDE requires further research.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.01.016.

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