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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 at 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 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. Epinephrine compared with all pooled treatments, was associated with a better survival rate to hospital discharge (RR: 1.16, 95% CI: 1.00–1.35) and a favorable neurologic outcome (RR: 1.24, 95% CI: 1.04–1.48). No difference was found in survival to hospital admission (RR: 1.02, 95% CI: 0.75–1.38) and ROSC when comparing epinephrine with all pooled treatments (RR: 1.13, 95% CI: 0.84–1.53). When epinephrine was compared with a placebo/no drugs, survival to hospital discharge (RR: 1.35, 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. However, there was not a favorable neurologic outcome (RR: 1.22, 95% CI: 0.99–1.51).

Conclusions: In OHCA, standard or high doses of epinephrine should be used because they improved survival to hospital discharge and resulted in a meaningful clinical outcome. There was also a clear advantage of using epinephrine over a placebo or no drugs in the composite 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) ranged from 8% to 10%.[1] Several factors affected the hospital survival, such as cardiopulmonary resuscitation of good quality and adequate post-resuscitation care. Standardized algorithms for advanced life support (ALS) and post-resuscitation care have been implemented in the European guidelines for resuscitation.[2] The last guideline regarding ALS recommends using

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https://doi.org/10.1016/j.resuscitation.2019.01.016

Received 22 September 2018; Received in revised form 13 January 2019; Accepted 14 January 2019

epinephrine (1 mg) every 3–5 min until return of spontaneous circulation (ROSC) is achieved. Actually, 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 is 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 and a positive neurologic outcome.[2] Recently, the PARAMEDIC2 trial showed that epinephrine in OHCA was associated with a slight improvement in the 30-day survival, b several survivors experienced a severe neurologic impairm

The aim of t ystem review and meta-analysis was to evaluate the ctiv ss pinephrine, compared with control treatments, on survi at admissi ROSC, survival at discharge, and a beneficial neu gic outc in ult patients during OHCA. Because we found the re di nt control treatments during OHCA, we plann a pri compar ons) to do a sub-analysis, dividing the studie cording to (1) th atments used in the control groups, which were placebo/no d high dose of epinephrine and epinephrine plus vasopres and (2) the fragility index, which was calculated on the pri outcome d red by each study.

Methods

This meta-analysis is registered with PROSPERO (n 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 the controls. The electronic search strategy was applied with standard filters for identification of the 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 the standard dose of epinephrine (SDE) versus all the pooled treatments, SDE versus a placebo or no drugs, SDE versus a high dose of epinephrine (HDE) >1 mg per dose, and SDE versus epinephrine + vasopressin. We compared the SDE with all pooled treatments because data on the effectiveness of this drug during OHCA come from conflicting studies. All pooled treatments consisted of a placebo or no drugs, HDE, and epinephrine + vasopressin.

Outcome

The primary outcome was the survival to hospital discharge after OHCA. The secondary outcomes were the return of spontaneous circulation (ROSC), survival to hospital admission and a good neurologic outcome. A good neurologic 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 score of 1 and 2, and a normal or moderate disability at the 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 potentially 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 roach. The quality evaluation included (1) the use of domization sequence generation, (2) the reporting of allocation oncealment, (3) blinding, (4) reporting incomplete outcome data, and (5) arability of the groups at the baseline. We solved any pos e disag ement by consensus through consultation with an e nal revie , if needed. We further calculated the fragility in x (FI) for each dy to assess its robustness. The FI was ca ted on the varia s that each study declared as a primary outcome/s.

Quantitative ysis

This meta-analysis wa ed ac rding to PRISMA guidelines.[4] A mixed rand effect the D Simonian and Laird method was used in meta-an s. he results were graphically represented with rest p graphs. e Relative Risk (RR) and 95% CI for each outcon ere separa y calculated for each trial with grouped data using intenti o-treat principle. The choice to use RR was driven by the 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 comparisons) to do a sub-analysis to analyze all the outcomes according to the following categories when possible: SDE versus all pooled treatments (all pooled treatments included a placebo/no drugs, HDE and epinephrine + vasopressin), SDE versus a placebo/no drugs, SDE versus 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 MetaAnalyst (version 6) and SPSS version 20 (IBM).

To evaluate 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 cases in comparison to other publication bias tests.[6]

Result

Study selection

A total of 1986 studies were identified, and 783 were duplicated; 108 full-text articles were assessed for eligibility; and 15 RCTs, involving 20 716 patients, were finally included in the analysis.[7–21] Fig. 1 illustrates the flow diagram of included studies.

Characteristics of the included study

Patients with OHCA were randomized to receive SDE versus a placebo/no drugs in three studies.[7–9] Six studies randomly compared patients receiving SDE versus HDE,[10–15] whereas six studies compared SDE versus Epi + Vaso.[16–21] Five studies considered more than one primary outcome.[11,13,15,16,18]. According to the FI, only three studies had an FI > 0.[8,11,15] The Table 1 Supplementary materials reported the characteristics of the included studies.

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

The SDE improved survival to hospital discharge when compared with all the pooled treatments (SDE versus all, RR: 1.16, 95% CI: 1.00–1.35, p = 0.04) and with a placebo/no drugs (SDE versus a placebo/no drugs, RR: 1.34, 95% CI: 1.08–1.67, p = 0.00). These results were confirmed also by the analysis including robust and not-robust trials (SDE FI > 0 versus control, RR: 1.32, 95% CI: 1.06–

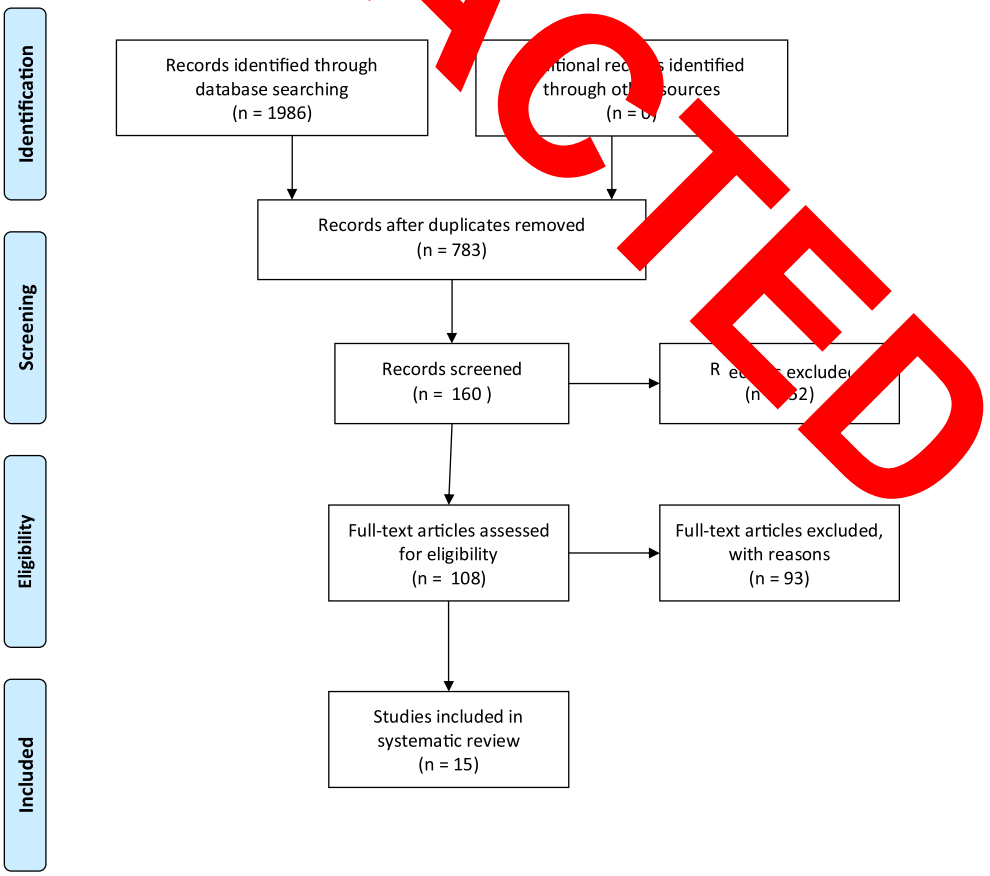

Fig. 1 – PRISMA flow diagram of included studies.

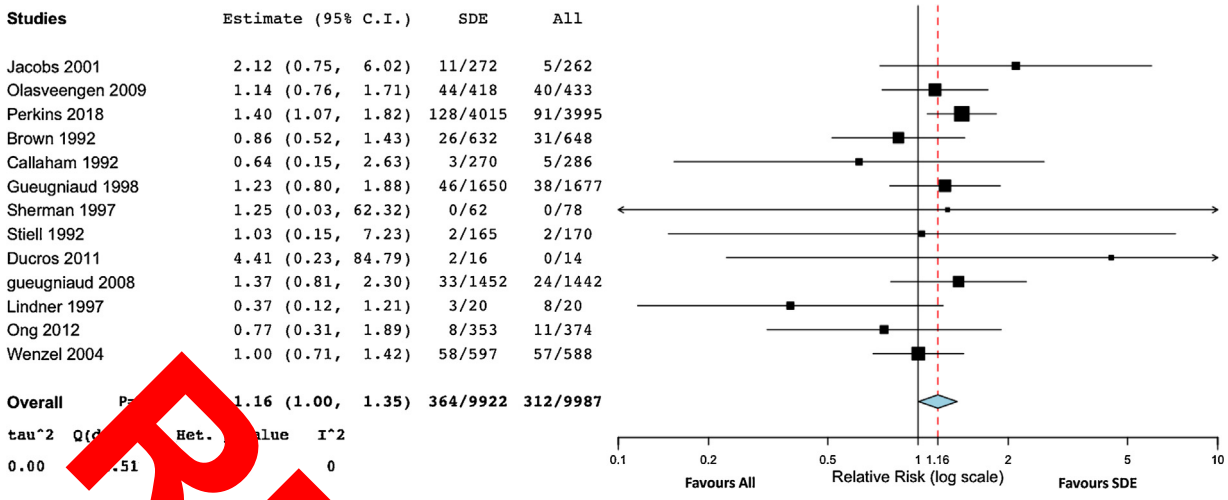

Fig. 2 – Forest pl or su al t e hospital discharge comparing SDE versus all the pooled treatment. Weights Jacobs: 2.02% eengo 13.30%, Perkins: 31.27%, Brown: 8.46% Callaham: 1.08%, Gueugniaud: 12.21%, Sherman: 0.14%, St 0.57% Ducr 0.25%, Gueugniaud: 8.10%, Lindner: 1.59%, Ong: 2.72%, Wenzel: 18.22%. Values were presente relative risk a 95% CI. SDE: standard dose of epinephrine.

1.65, p = 0.01; SDE FI = 0 versus contro RR: 1.05, CI: 36 – 1.28, p = 0.63).

There was no difference in survival to hos disc n comparing the SDE with the HDE (SDE versus HDE, RR 03, 95% CI: 0.75 – 1.41, p = 0.80) and the SDE with Epi + Vaso E versus Epi + Vaso, RR: 0.99, 95% CI: 0.69 – 1.43, p = 0.99). Fig. 2 sho forest plot for the survival to hospital admission.

Secondary outcomes

No difference was found in the ROSC when comparing the SDE with all the pooled treatments (SDE versus all, RR: 1.14, 95% CI: 0.84–1.53, p = 0.40). The SDE improved the ROSC when compared with a 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). There was no difference in the of ROSC between the SDE and the Epi + Vaso (SDE versus + Vaso, RR: 1.02, 95% CI: 0.91–1.14, p = 0.71). Fig. 3 shows the rest plot for the ROSC. There was no difference in the ROSC, even in the an including the robust and the not-robust RCTs (SDE FI ersus trol, RR: 1.21, 95% CI: 0.46–3.20, p = 0.69; SDE F versus co ol, RR: 1.10, 95% CI: 0.93–1.29, p = 0.23).

Survival to hospit dmission was not reduced in patients treated wit SDE when co red with all the pooled treatments (SDE versus all, RR: 1.02, 9 75–1.38, p = 0.88), even if the analysis

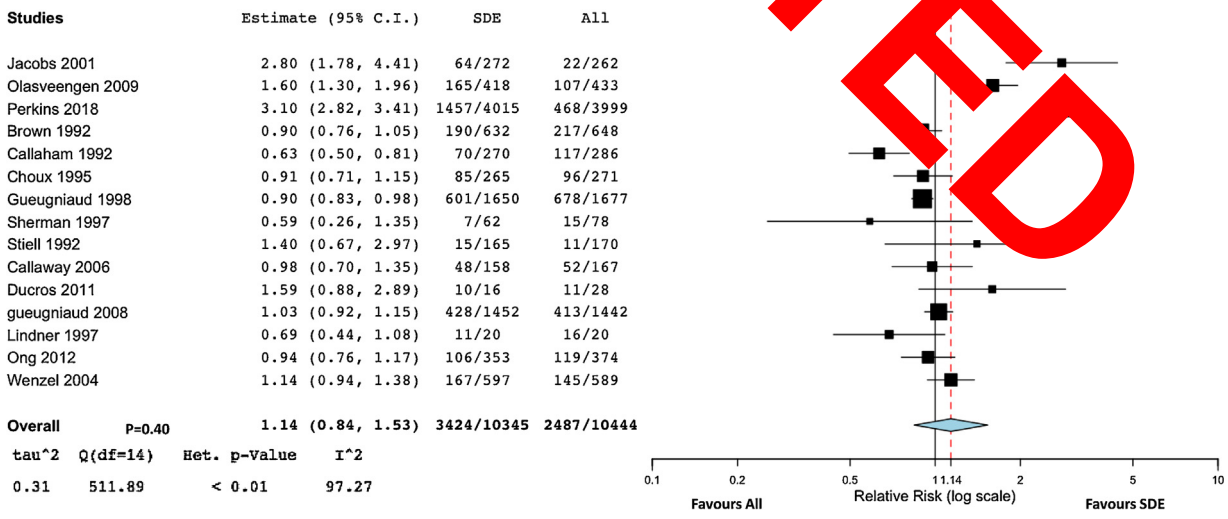

Fig. 3 – Forest plot for ROSC comparing SDE versus all the pooled treatment. Weights: Jacobs: 6.33%, Olasveengen: 7.17%, Perkins: 7.36%, Brown: 7.26%, Callaham: 7.06%, Choux: 7.08%, Gueugniaud: 7.37%, Sherman: 4.71%, Stiell: 5.06%, Callaway: 6.81%, Ducros: 5.72%, Gueugniaud: 7.33%, Lindner: 6.34%, Ong: 7.13%, Wenzel: 7.20%. Values were presented as relative risk and 95% CI. SDE: standard dose of epinephrine.

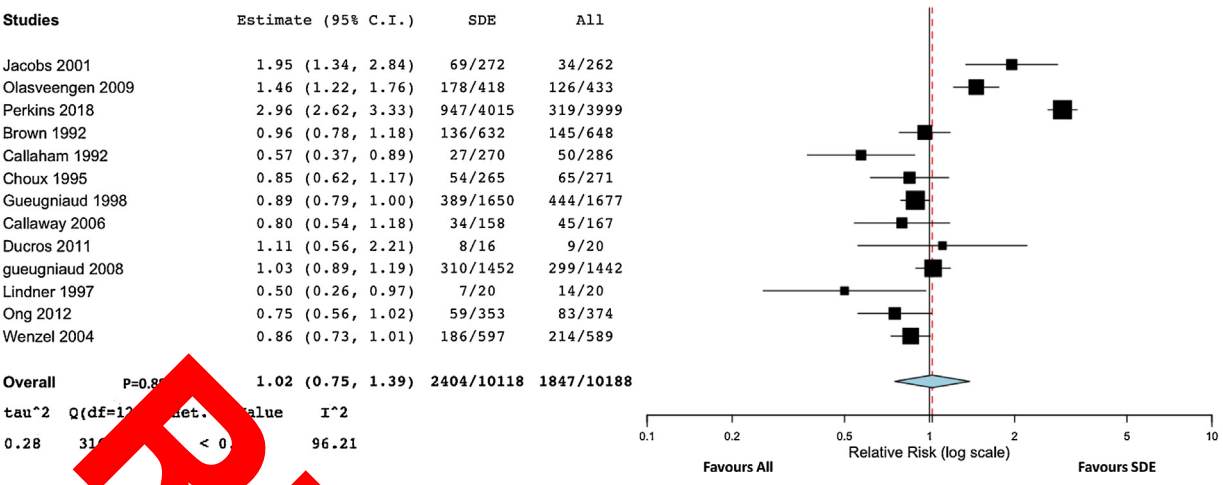

Fig. 4 – Forest plot for survival to the hospital admission comparing SDE with all the pooled treatment. Weights: Jacobs: 8.55%, Olasveengen: 8.26%, Perkins: 8.41%, Brown: 8.20%, Callaham: 7.25%, Choux: 7.80%, Gueugniaud: 8.42%, Callaway: 8.48%, Ducros: 5.93%, Gueugniaud: 8.37%, Lindner: 6.07%, Ong: 7.87%, Wenzel: 8.33%. Values were presented as relative risk and 95% CI. SDE: standard dose of epinephrine.

of robust RCTs found an improvement in the result (SDE versus control, RR: 2.04, 95% CI: 1.22–3.43, p = 0.06). The 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). No difference in survival to hospital admission was found when comparing the SDE with the Epi + Vaso (SDE versus Epi + Vaso, RR: 0.87, 95% CI: 0.74–1.01, p = 0.07). Fig. 4 demonstrates the forest plot for the survival to hospital admission.

The SDE increased the rate of patients discharged with a good neurologic outcome when compared with all the pooled treatments (SDE versus all, RR: 1.66, 95% CI: 1.00–1.35, p = 0.04) and in the not-robust trials (SDE FI = 0 versus control, RR: 1.29, 95% CI: 1.02–1.64, p = 0.02). There was no difference in patients discharged with a favorable neurologic outcome when comparing the SDE with a placebo/no drugs (SDE versus a placebo/no drugs, RR: 1.22, 95% CI: 0.99–1.52, p = 0.06), when comparing the SDE with the HDE (SDE versus HDE, RR: 1.20, 95% CI: 0.73–1.95, p = 0.45), when comparing SDE with the 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). Fig. 5 illustrates the forest plot for a positive neurologic outcome.

Discussion

In this systematic review and meta-analysis including 20 716 patients treated with epinephrine during OHCA, we found that epinephrine, when compared to all pooled treatments, improved the survival to hospital discharge and good neurologic outcome,

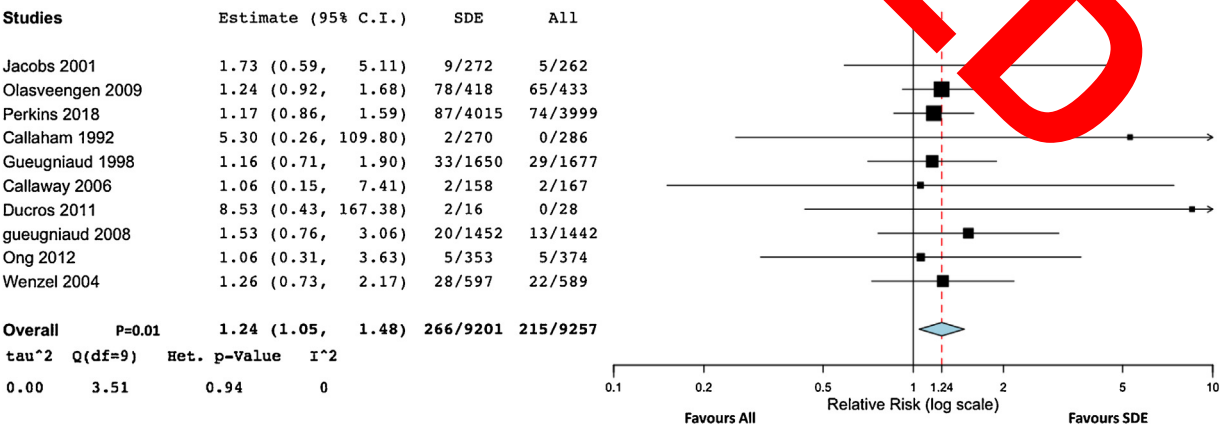

Fig. 5 – Forest plot for the good neurologic outcome comparing SDE versus all the pooled treatment. Weights: Jacobs: 2.58%, Olasveengen: 33.34%, Perkins: 31.97%, Callaham: 0.32%, Gueugniaud: 12.32%, Callaway: 0.79%, Ducros: 0.34%, Gueugniaud: 6.24%, Ong: 1.98%, Wenzel: 10.07%. Values were presented as relative risk and 95% CI. SDE: standard dose of epinephrine.

but did not increase the ROSC and the survival to hospital admission. In the subgroup analyses we found that (1) the survival to hospital discharge, ROSC, and survival to hospital admission increased when epinephrine was compared with a placebo/no drugs; (2) there were no differences in the considered outcomes between epinephrine and epinephrine plus vasopressin; (3) a high dose of epinephrine ameliorated the ROSC and the survival to hospital admission but had the same effect as a standard dose of epinephrine on the survival to hospital discharge and a good neurologic outcome; and (4) considering the robust RCTs, epinephrine increased the short- and long-term survivals but did not improve the secondary outcomes.

To our knowledge, this is the first meta-analysis that (1) compares epinephrine with placebo/no drugs; (2) stratifies the RCTs according to the FI; and (3) includes the study by Perkins et al.[9] Recently, Zhang et al. performed a systematic review and meta-analysis comparing epinephrine with epinephrine plus vasopressin and including Asian, American, and European studies.[22] Interestingly, Zhang et al. found that epinephrine improved ROSC only in Asian patients, and not in European and American patients.[22] However, Asian RCTs had very poor quality, and the meta-analysis possessed a high heterogeneity.[22]

Lin et al. performed a subgroup analysis of the RCT comparing epinephrine with a high dose of epinephrine, and epinephrine with epinephrine plus vasopressin.[23] This meta-analysis did not include the study by Perkins et al.[9]; actually, they did not perform any forest plot between epinephrine and a placebo/no drugs.[23] Two previous meta-analyses, including RCTs and observational studies, found that epinephrine was not effective at increasing the survival to hospital discharge.[24,25] Our pooled results were very different from the previous reviews,[23–25] because we found a better survival to hospital discharge and a meaningful neurologic outcome by using epinephrine in OHCA.

Previous medical literature reported that epinephrine versus a placebo was associated with a significant improvement in the ROSC and the survival to hospital admission, but no difference was found in the survival to hospital discharge and a favorable neurologic outcome.[26] Even the recent study by Perkins et al., the PARAMEDIC trial,[9] showed that epinephrine, when compared with a placebo, and despite having a powerful effect on the ROSC after OHCA, produced only a small absolute increase in survival and no improvement in a favorable functional recovery. In this view, the results of the present meta-analysis may be groundbreaking, because epinephrine, when compared with a placebo/no drugs, improved short-term and long-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 due to the in-hospital management and therapies that are increased for several days after OHCA.[27] Optimizing the respiratory and cardiac functions after cardiac arrest may improve long-term outcomes beyond the use of epinephrine during OHCA.[28]

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.[26]

A systematic review, a meta-analysis, and the RCTs top the list of the level of evidence.[29] The RCTs included in the meta-analyses are currently screened for methodological quality in order to search for the risk of bias.[29] Recently, the FI was introduced in critical care literature, with the purpose of measuring the robustness of RCTs from a statistical point of view.[30] According to the current definition, RCTs with a larger FI have more robust findings when compared with the studies with a poor FI.[30] An FI was never applied to the meta-analysis.[31] Because a low FI in critical care trials reinforced the finding that the robustness of evidence available to clinical decision makers in this setting 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. Probably, an FI may add more robustness to the results of the present meta-analysis. Nevertheless, the use of an FI in meta-analysis should be implemented by future literature. In line with previous systematic reviews,[23] 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 with guidelines for cardiac arrest that are reported to be still in debate.[2] Second, we found high heterogeneity ($>50\%$ in 13 out of 24 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.

Conclusions

In OHCA, standard or high doses of epinephrine should be used, because they improve survival to hospital discharge and meaningful clinical outcome. There is also a clear advantage of using epinephrine over a placebo or no drugs for the considered outcomes. Further trials are needed to assess the best dose of epinephrine for OHCA, because the optimal dose of epinephrine is still unknown. According to our data reporting that a high dose of epinephrine was associated with better ROSC and survival to hospital admission, future research should investigate this point.

Conflict of interest

None.

Funding

The authors received no financial support for this study.

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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