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Antiarrhythmics in Cardiac Arrest: A Systematic Review and Meta-Analysis

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Introduction

It is widely accepted that antiarrhythmics play a role in cardiopulmonary resuscitation (CPR) universally, but the absolute benefit of antiarrhythmic use and the drug of choice in advanced life support remains controversial.

Aim

To perform a thorough, in-depth review and analysis of current literature to assess the efficacy of antiarrhythmics in advanced life support.

Material and Methods

Two authors systematically searched through multiple bibliographic databases including CINAHL, SCOPUS, PubMed, Web of Science, Medline(Ovid) and the Cochrane Clinical Trials Registry. To be included studies had to compare an antiarrhythmic to either a control group, placebo or another antiarrhythmic in adult cardiac arrests. These studies were independently screened for outcomes in cardiac arrest assessing the effect of antiarrhythmics on return of spontaneous circulation (ROSC), survival and neurological outcomes. Data was extracted independently, compared for homogeneity and level of evidence was evaluated using the Cochrane Collaboration's tool for assessing the risk of bias. The Mantel-Haenszel (M-H) random effects model was used and heterogeneity was assessed using the I^2 statistic.

Results and Discussion

The search of the literature yielded 30 studies, including 39,914 patients. Eight antiarrhythmic agents were identified. Amiodarone and lidocaine, the two most commonly used agents, showed no significant effect on any outcome either against placebo or each other. Small low quality studies showed benefits in isolated outcomes with esmolol and bretylium against placebo. The only significant benefit of one antiarrhythmic over another was demonstrated with nifekalant over lidocaine for survival to admission ($p = 0.003$). On sensitivity analysis of a small number of high quality level one RCTs, both amiodarone and lidocaine had a significant increase in survival to admission, with no effect on survival to discharge.

Conclusions

This systematic review and meta-analysis suggests that, based on current literature and data, there has been no conclusive evidence that any antiarrhythmic agents improve rates of ROSC, survival to admission, survival to discharge or neurological outcomes. Given the side effects of some of these agents, we recommend further research into their utility in current cardiopulmonary resuscitation guidelines.

Keywords

Cardiac arrest • Antiarrhythmics • Cardiopulmonary resuscitation • Ventricular fibrillation

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Introduction

Q5 Out-of-hospital cardiac arrests (OHCAs) have a reported incidence of 395,000 events in the US with only 5.5% of patients surviving to hospital discharge, whilst in-hospital cardiac arrests (IHCA) have an estimated incidence of 200,000 in the US with 24.4% surviving to discharge [1,2]. High mortality rates and associated complications such as irreversible neurological disability explain the significant public health burden of cardiac arrest [2,3]. Thus, the need for a standardised approach to resuscitation to improve cardiac and cerebral perfusion during cardiopulmonary resuscitation (CPR) has been recognised for many years, with the aim of improving cardiac arrest outcomes [3].

Pharmacological therapy is universally employed as a resuscitative measure to enhance myocardial perfusion pressure and peripheral blood flow and additionally improve defibrillation success. Antiarrhythmics (AAs) play a role in shock-refractory ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT) in the restoration and maintenance of a spontaneous perfusing rhythm during shock termination [4,5]. The American Heart Association (AHA) guidelines recommend the use of AA agents, however there is limited evidence on the associated short-term and long-term outcomes [4-8].

In light of this, we conducted a systematic review and meta-analysis to appraise randomised controlled trials and cohort studies around the efficacy of AAs in adult cardiac arrest, and their effects on short- and long-term patient outcomes.

Methods

Search Strategy

A systematic search was conducted on multiple bibliographic databases including CINAHL, SCOPUS, PubMed, Web of Science, The Cochrane Trials Registry and Medline (Ovid) from the inception of the databases until December 2016. Two independent reviewers used the following combinations of search terms (1) ("Cardiac Arrest") OR ("Cardiac Arrhythmias") OR ("Cardiopulmonary Resuscitation") OR ("Ventricular Tachycardia") OR ("Ventricular Fibrillation") OR ("Advanced Life Support")) AND ("Antiarrhythmics") OR ("Antiarrhythmia agents") OR ("Amiodarone") OR ("Lignocaine") OR ("Lidocaine") OR ("Magnesium") OR ("Potassium-channel blockers"). For completeness, a manual reference check of systematic reviews and recent articles was performed to identify any additional studies.

Inclusion Criteria

For a study to be included, the patient population was any adult (over 18 years of age) with a cardiac arrest, either an OHCA or IHCA. All AA agents were considered as an intervention including amiodarone, lidocaine, magnesium, in addition to potassium-channel blockers such as nifekalant

and bretylium in comparison to a placebo. Outcomes that were measured included ROSC; short-term survival: survival to hospital admission for OHCA patients, survival to hospital discharge; and neurologic outcomes at discharge. Study designs were limited to randomised controlled trials (RCTs) or prospective/retrospective cohort designs. Two reviewers (AC and BF) assessed and agreed upon each study for inclusion in this systematic review and any discrepancies were discussed with LW and TM.

Data Extraction

Two reviewers (AC and BF) independently extracted data from each article that met the inclusion criteria. The data extracted from each study included the first author's last name and publication year, the study design, number of participants, patient population, intervention and clinical outcome results. The data collected by each reviewer was then compared for homogeneity and any discrepancies were addressed by discussion with LW and TM.

Level of Evidence and Risk of Bias

Each article was evaluated using the Centre for Evidence Based Medicine (CEBM): Levels of Evidence Introduction Document [9]. These studies were then assessed for risk of bias and methodological quality using the Cochrane Collaboration's tool for assessing the risk of bias [10]. The results from each study were then grouped into individual AAs.

Statistical Analyses

The combined data was analysed using RevMan 5.3 software (The Nordic Cochrane Centre, Copenhagen, Denmark). The odds ratio (OR) with 95% confidence interval (CI) was used for dichotomous outcomes, and the weighted mean difference (WMD) with 95% CI for continuous outcomes. The Mantel-Haenszel (M-H) random effects model was used. Heterogeneity was assessed using the I^2 statistic, with an $I^2 > 50\%$ indicating significant heterogeneity. P value of < 0.05 provided evidence of significant OR and WMD. We then conducted sensitivity analyses to assess how variance in rhythms and location of cardiac arrest may affect our results. As part of the sensitivity analysis, each outcome was also analysed using only level one RCTs.

Results

Literature Search Results

The initial systematic literature search yielded 1110 citations, of which 340 abstracts were reviewed. Based on a review of their abstract, 54 articles appeared to meet the search criteria. Of these 54 articles, 31 met the inclusion criteria (Figure 1). These 31 articles included eight intervention medications and 42,808 patients (Appendix 1). Each study was then screened for risk of bias and methodological quality (Figure 2). Of these, 11 were high quality level one RCTs, two were low

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