International Journal of Cardiology 221 (2016) 780–788

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

Amiodarone and cardiac arrest: Systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 21 May 2016
Accepted 8 July 2016
Available online 9 July 2016

Keywords:
Cardiac arrest
Cardiopulmonary resuscitation
Amiodarone
Systematic review
Meta-analysis

ABSTRACT

Introduction: The 2015 Guidelines for Resuscitation recommend amiodarone as the antiarrhythmic drug of choice in the treatment of resistant ventricular fibrillation or pulseless ventricular tachycardia. We reviewed the effects of amiodarone on survival and neurological outcome after cardiac arrest.
Methods: We systematically searched MEDLINE and Cochrane Library from 1940 to March 2016 without language restrictions. Randomized control trials (RCTs) and observational studies were selected.
Results: Our search initially identified 1663 studies, 1458 from MEDLINE and 205 from Cochrane Library. Of them, 4 randomized controlled studies and 6 observational studies met the inclusion criteria and were selected for further review. Three randomized studies were included in the meta-analysis. Amiodarone significantly improves survival to hospital admission (OR = 1.402, 95% CI: 1.068–1.840, $Z = 2.43$, $P = 0.015$), but neither survival to hospital discharge (RR = 0.850, 95% CI: 0.631–1.144, $Z = 1.07$, $P = 0.284$) nor neurological outcome compared to placebo or nifekalant (OR = 1.114, 95% CI: 0.923–1.345, $Z = 1.12$, $P = 0.475$).
Conclusions: Amiodarone significantly improves survival to hospital admission. However there is no benefit of amiodarone in survival to discharge or neurological outcomes compared to placebo or other antiarrhythmics.

1. Introduction

In Europe, the incidence of sudden cardiac arrest (SCA) is estimated 0.4–1 per 1000 inhabitants per year, thus involving between 350,000 and 700,000 people [1–3]. In North America, the annual incidence of out-of-hospital cardiac arrest (OHCA) is 50–55 per 100,000 people and that of in-hospital cardiac arrest (IHCA) ranges from 3 to 6 per 1000 admissions [4]. Out-of-hospital cardiac arrest is the third leading cause of death in the USA. Unfortunately, resuscitation attempts are unsuccessful in most cases, while less than 10% of cardiac arrest victims survive to hospital discharge [5,6].

Although early defibrillation is highly effective for terminating ventricular fibrillation/pulseless ventricular tachycardia (VF/VT), it cannot prevent recurrences of VT/VF and antiarrhythmic drugs are commonly used [7–11]. Amiodarone is a Vaughan Williams class III antiarrhythmic drug which is currently recommended as the first-line drug for refractory VF/VT [12,13]. It has a complex mechanism of action with mechanistic properties that include action at a- and b-adrenergic receptors, as well as on potassium, sodium and calcium channels. It markedly prolongs action potential and repolarization while decreasing atrioventricular (AV) conduction and sinus node function [14].

Amiodarone's effectiveness in refractory VF/VT was established by two randomized double-blind studies, the ARREST and ALIVE trials, with both of these concluding that amiodarone had significantly higher rates of survival to admission to hospital [15,16]. Amiodarone also appears to improve the response to defibrillation when given to humans or animals with VF/VT. However, there is no evidence regarding the optimal time at which amiodarone should be given when using a single-shock strategy. In all clinical studies until now, amiodarone was given if VF/VT persisted after at least three shocks and in the absence of any other data, amiodarone is currently recommended at an initial dose of 300 mg followed by intravenous infusion.

Despite the advances in resuscitation drug research, there are limited data regarding the beneficial effects of amiodarone as far as hospital to discharge and neurological outcome are concerned in both OHCA and IHCA. This lack of evidence is reflected in the 2015 guidelines which

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http://dx.doi.org/10.1016/j.ijcard.2016.07.138
0167-5273/

state that during cardiac arrest uninterrupted, high-quality chest compressions and early defibrillation for VF/VT are of primary importance, while drug administration is of secondary importance [12,13]. The aim of this systematic review and meta-analysis is to assess the available evidence regarding the effects of amiodarone on survival and neurological outcome after cardiac arrest.

2. Methods

2.1. Eligibility criteria and search strategy

We identified eligible studies by searching MEDLINE via PUBMED and the Cochrane Library from 1940 to March 2016 without language restrictions (MEDLINE and Cochrane search terms in Appendices A and B, respectively). As no human subjects or medical records were reviewed in this study, institutional review board approval was not required. Our search strategy included relevant substance names, Medical Subject Heading and Entree terms. Keywords used included "cardiac arrest", "heart arrest", "sudden death", "cardiopulmonary resuscitation", "cardio-pulmonary resuscitation", "CPR", "ventricular fibrillation", "pulseless ventricular tachycardia", "pulseless electrical activity", "death, sudden", "heart arrest, induced", "amiodarone", "cordarone", "pacerone", "nexterone" and "angoron". In addition, we searched the following databases for unpublished or ongoing studies: http://www.controlled-trials.com and http://wwwclinicaltrials.gov. We also searched the reference lists of eligible articles and relevant reviews [17–19].

2.2. Study selection

Two independent reviewers (AL and AL) screened all potentially relevant titles and abstracts for eligibility. The remaining articles underwent full-text review; again, studies that that did not fit inclusion criteria were excluded. We identified studies according to the following criteria: randomized control designed or observational; children or adult human studies with either OHCA or IHCA; and the included studies should have been conducted according to the international resuscitation guidelines. In addition, the included studies should have reported one of the following outcomes: return of spontaneous circulation (ROSC); short-term survival: survival to hospital intensive care unit admission for out-of-hospital patients and 24 h survival for in-hospital patients; survival to hospital discharge; and neurologic outcome at hospital discharge. Neurological outcome was assessed using the Glasgow Outcome Scale (GOS) which classifies physical functioning capacity into 5 stages: grade 5 — good recovery (returns to normal life), grade 4 — moderate disability (independent), grade 3 — severe disability (depends on care), grade 2 — vegetative stage, and grade 1 — death [20].

The authors completed the literature search and selected by consensus the studies based on inclusion criteria as judged by title, abstract, and complete manuscript. Intrarater reliability was measured with a 10% sample of citations, resulting in a kappa of 0.91. Each article with conflicting opinion from the two initial reviewers was discussed with another reviewer (DO) for a final resolution. The selected studies compared amiodarone to placebo or other antiarrhythmic drugs (lidocaine and nifekalant).

We included four randomized controlled trials that compared amiodarone to placebo, lidocaine or nifekalant in adults with OHCA and shock-resistant VF. We also included retrospective observational studies comparing amiodarone either with placebo or other antiarrhythmic drugs (lidocaine and nifekalant). Publications retrieved from electronic databases were imported into reference management software (EndNoteX6, Thomson Reuters, New York, USA).

2.3. Data extraction and quality assessment

Data extraction was performed independently by two reviewers (AL and AL). For each eligible trial we extracted data on study characteristics, participants' baseline characteristics, and outcomes regarding ROSC, short-term survival, survival to discharge and neurological function. Missing data were requested via e-mails to corresponding authors.

For each eligible study, we recorded odds ratios (ORs) and hazard ratios (HRs) and corresponding 95% confidence intervals as indexes of the effect size of amiodarone. Numeric data for effect size or the ratio of the number of patients that experienced the endpoint among cases and controls were used from the selected articles.

Two reviewers independently assessed risk of bias of each study using the Cochrane Collaboration risk-of-bias tool (Table 1) [21]. We assessed each trial across the following quality domains: a) random-sequence generation; b) allocation concealment; c) blinding; d) incomplete outcome data; and e) selective outcome reporting or other potential threats to validity. Disagreements were discussed with another reviewer (DO) and resolved by consensus.

In the randomized trials conducted by Kudenchuk et al. in 1999 and 2016 complete randomization and adequate blinding were performed and the rescuers were blinded as well throughout the trials, so low risk of bias was considered across the studies [16,22]. In the study of Dorian et al. although sequence generation was not reported in the text, randomization was used and allocation concealment as well as blinding were considered to be adequately performed [15]. As a result, low risk of bias was considered. In the study by Amino et al. unclear risk of allocation bias was considered [23]. Also, performance and detection bias was considered as well regarding the high risk of selection in observational studies. The rest of the studies as observational ones were assessed with high risk of bias as they lack randomization, allocation concealment and blinding [24–29].

2.4. Statistical analysis

The risk estimates of each study were treated as ORs. In order to provide a more meaningful effect size, we compared amiodarone vs. all other alternative treatments (i.e. nifekalant or lidocaine or placebo). Neurological outcomes were grouped into two categories of good recovery and severe disability and measured as ORs with 95% CIs as well adapted for meta-analysis.

We performed a meta-analysis of studies investigating the effect of administering amiodarone in terms of cardiac arrest to obtain the pooled estimate separately for: 1) ROSC, 2) survival to hospital admission, 3) 24 h survival, 4) survival to hospital discharge, and 5) neurological outcome. Heterogeneity was tested by using the I^2 statistical method ($I^2 < 20\%$ low, $20\% < I^2 < 60\%$ moderate, and $I^2 > 60\%$ high) [30]. Moderate to significant heterogeneity ($P < 0.1$) existed among studies and a random effects model was subsequently implemented using the DerSimonian & Laird method with the estimate of heterogeneity being taken from the inverse-variance. To test whether the true effect in all studies is the same (i.e. heterogeneity), we used the I-squared measure I^2 that permits quantification of discrepancy among studies. We conducted a between-study subgroup analysis to evaluate whether the estimates of the effect of amiodarone on study main endpoints differ within certain populations (OHCA vs. IHCA, short vs. long duration CPR, initial shockable rhythm, short duration (<10 min) vs. long (>10 min) duration of ALS, early (<24 min) vs. delayed (>24 min administration of amiodarone after cardiac arrest)). A gender subgroup analysis was not feasible since all but one study [25] reported that the percentage of males among subjects with cardiac arrest exceeded 65%. Differences in pooled effect sizes between subgroups were compared with a test of interaction (Cochran's Q test). The mean effect size and confidence intervals (CIs) of individual studies were illustrated with forest plots. To estimate the contribution of continuous study moderators to the overall heterogeneity, random-effects meta-regression was performed.

The presence of publication bias was investigated graphically by funnel plots of precision and statistically by regression tests for asymmetry. The Egger test as well as the Begg & Mazumdar test were implemented and performed a linear regression of the intervention effect estimates on their standard errors weighting by 1/(variance of the intervention effect estimate).

Statistical analysis was performed with STATA package, version 11.1 (StataCorp, College Station, Texas, USA). The module "metan" was used for meta-analysis. We deemed statistical significance at $P < 0.05$.

3. Results

Our search in literature initially identified 1663 studies, 1458 from MEDLINE and 205 from Cochrane Library. Of them, 4 randomized controlled studies and 6 observational studies met the inclusion criteria and were selected for further review (Fig. 1).

3.1. Study characteristics

Table 2 presents the characteristics of the included studies. Seven studies reported interventions after adult OHCA, while 3 studies report interventions after adult IHCA. Only one study included children as participants. Three categories were identified: amiodarone vs. placebo, amiodarone vs. lidocaine, and amiodarone vs. nifekalant and were grouped as amiodarone vs. alternative treatment in order to derive more reliably the effect size of amiodarone towards cardiac arrest in the current meta-analysis.

The meta-analysis included 10 studies and a total of 5326 patients (2162 subjects received amiodarone, 1422 received placebo, 1666 received lidocaine, and 76 received nifekalant) (Table 2). Studies that were incorporated in the meta-analysis were published since 1999. Corresponding sample sizes ranged from 25 to 3026 individuals. For individuals that were treated with amiodarone, median age was 64.7 years and 75.8% of the population was male, while 78.4% of the patients in the amiodarone arm and 73.9% in the alternative treatment arm presented previous history of cardiac disease.

3.2. Return of spontaneous circulation

Seven out of 10 studies reported ROSC. Administration of amiodarone tended to decrease the odds for ROSC by 22% (OR = 0.780, 95% CI: 0.574–1.059, $Z = 1.59$, $P = 0.112$) (Fig. 2A). Moderate to significant heterogeneity was observed across the studies ($I^2 = 51.4\%$,