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Review article

Amiodarone or lidocaine for cardiac arrest: A systematic review and meta-analysis☆

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ABSTRACT

Background: Guidelines for treatment of out-of-hospital cardiac arrest (OOH-CA) with shockable rhythm recommend amiodarone, while lidocaine may be used if amiodarone is not available. Recent underpowered evidence suggests that amiodarone, lidocaine or placebo are equivalent with respect to survival at hospital discharge, but amiodarone and lidocaine showed higher hospital admission rates. We undertook a systematic review and meta-analysis to assess efficacy of amiodarone vs lidocaine vs placebo.
Methods: We included studies published in PubMed and EMBASE databases from inception until May 15th, 2016. The primary outcomes were survival at hospital admission and discharge in OOH-CA patients enrolled in randomized clinical trials (RCT) according to resuscitation with amiodarone vs lidocaine vs placebo. If feasible, secondary analysis was performed including in the analysis also patients with in-hospital CA and data from non-RCT.
Results: A total of seven findings were included in the metanalysis (three RCTs, 4 non-RCTs). Amiodarone was as beneficial as lidocaine for survival at hospital admission (primary analysis odds ratio—OR 0.86–1.23, $p = 0.40$) and discharge (primary analysis OR 0.87–1.30, $p = 0.56$; secondary analysis OR 0.86–1.27, $p = 0.67$). As compared with placebo, survival at hospital admission was higher both for amiodarone (primary analysis OR 1.12–1.54, $p < 0.0001$; secondary analysis OR 1.07–1.45, $p < 0.005$) and lidocaine (secondary analysis only OR 1.14–1.58, $p = 0.0005$). With regards to hospital discharge there were no differences between placebo and amiodarone (primary outcome OR 0.98–1.44, $p = 0.08$; secondary outcome OR 0.92–1.33, $p = 0.28$) or lidocaine (secondary outcome only OR 0.97–1.45, $p = 0.10$).
Conclusions: Amiodarone and lidocaine equally improve survival at hospital admission as compared with placebo. However, neither amiodarone nor lidocaine improve long-term outcome.

Introduction

Sudden cardiac arrest (CA) is an emergency with high incidence ranging between 320,000 and 700,000 events per year in the United States and Europe.[1,2] Among out-of-hospital (OOH) CA, survival at hospital admission is approximately 35–40%,[3,4] while at hospital discharge is much lower (8–24%).[3–8] Importantly, favorable neurological outcome is reported only in less than half of patients admitted to ICU after return of spontaneous circulation (ROSC).[9,10]

The recent guidelines for the treatment of OOH-CA with a shockable rhythm (ventricular fibrillation – VF – or pulseless ventricular tachycardia – VT –) suggest only amiodarone as antiarrhythmic drug after three defibrillation attempts, while lidocaine may be used as alternative, if amiodarone is not available.[11,12] However, in a recent randomized controlled trial (RCT) amiodarone, lidocaine or placebo had similar results, although the RCT was possibly underpowered. Interestingly, amiodarone and lidocaine showed a significantly higher number of patients admitted alive to the hospital, and a higher survival at hospital discharge in the subgroup of

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Table 1
"PICOS" approach for selecting clinical studies in the systematic search and meta-analysis. CA: cardiac arrest; VF: ventricular fibrillation; VT: ventricular tachycardia (pulseless).

PICOS	
1. Participants	Patients in CA with a shockable rhythm (VF/VT), including both in- and out-of-hospital setting
2. Intervention	Administration of amiodarone
3. Comparison	Placebo, lidocaine (primary analysis); no drug administered (secondary analysis)
4. Outcomes	Survival at hospital admission; survival at hospital discharge; favorable neurological outcome (modified Rankin scale score ≤3 or return to independent living activities)
5. Study design	RCT (primary analysis); prospective and retrospective studies (secondary analysis)

patients with bystander-witnessed CA. Before this RCT, a recent meta-analysis analyzed the efficacy of anti-arrhythmic drugs in the treatment of CA,[13] but it included drugs not currently recommended and suffered from large biases in the studies included. For instance, many of these studies were retrospective chart reviews, with unbalanced baseline characteristics,[14] or different timing of drug administration and severely under-dosed treatments.[15]

To overcome such limitations and in view of the recently published large RCT, we conducted a meta-analysis aiming at assessing the efficacy of amiodarone as compared with lidocaine or placebo.

Methods

Search strategy and criteria

We undertook a systematic web-based advanced literature search through the *NHS Library Evidence* tool on the effects of amiodarone in patients with CA. We followed the approach suggested by the PRISMA statement for reporting systematic reviews and meta-analyses[16] and a PRISMA checklist is provided separately (Supplemental digital content 1).

An initial computerized search of MEDLINE (PubMed) was conducted from inception until April 10th, 2016 to identify the relevant articles. With these findings, we wrote a draft of the prospective study protocol. A final search was re-performed at the end of the analysis (May 15th, 2016) to identify further findings. Our core search was structured by combining a group of findings containing the term "cardiac arrest" or "hear arrest" with a second group including the word "amiodarone" and/or "lidocaine". Two further searches were performed manually combining the words "amiodarone" and "cardiac arrest" or "lidocaine" and "cardiac arrest". Inclusion criteria were pre-specified according to the PICOS approach (Table 1).

We a priori decided to consider a secondary analysis including non-randomized prospective and retrospective clinical studies. We excluded experimental animal studies, book chapters, reviews, editorials and letters to editor. Case series were not included in the secondary analysis unless reporting at least 10 patients per group. Study selection for determining the eligibility for inclusion in the systematic review and data extraction were performed independently by four reviewers (FS, CC, CS, AA). Discordances were resolved by involving the other three authors and/or by consensus. Language restrictions were applied: we read the full manuscript only for articles published in English, French, Spanish, German or Italian. For prospective and retrospective studies published in other languages, we read the abstract and, if necessary, contacted the authors for further information. A manual search was conducted independently by three authors (FS, CS, AA), exploring also the list of references of the findings of the systematic search.

Groups and endpoints

We primarily compared the efficacy of amiodarone vs lidocaine vs placebo with regards of survival at hospital admission and hospital discharge in patients with OOH-CA enrolled in RCTs. If available, the incidence of favorable neurological outcome (as defined by a modified Rankin scale score ≤3 or return to independent living activities) was assessed. A secondary analysis was performed including also results from non-RCTs and studies including patients suffering from in-hospital CA.

Quality assessment

Methodological quality of included RCTs was performed using the Cochrane Collaboration tool which incorporated the following domains: selection, performance, detection, attrition, performance and other potential sources of bias.[17] Risk of bias assessment for observational studies was performed using the Newcastle–Ottawa scale (NOS) which gives up to nine points if all criteria of quality assessment are fulfilled. The scale has three main domains and according to their score studies are classified at high risk (1–3 points), intermediate risk (4–5 points) and low risk of bias (6–9 points).[18–20]

Statistical analysis

The Mantel–Haenszel method was used to analyze dichotomous outcomes of survival at hospital admission and at hospital discharge and survival with good neurological outcome. Results are reported as odd ratios (OR) with 95% confidence intervals (CI) and two tailed p values. p values were considered significant if <0.05. The presence of statistical heterogeneity was assessed using the X2 (Cochran Q) test. Heterogeneity was likely if $Q > df$ (degrees of freedom) suggested and confirmed if $p \leq 0.10$. Quantification of heterogeneity was performed and values of I^2 ranging 0–24.9%, 25–49.9%, 50–74.9% and >75% were considered as none, low, moderate and high heterogeneity, respectively. If heterogeneity was quantified as low or above, a random-model was also used for sensitive analyses.[21]

Results

Our systematic search identified 528 findings via *NHS Library Evidence* search. No other findings were retrieved manually. As shown in the PRISMA flow diagram (Supplemental digital content 2), after the evaluation of all findings, only seven studies were judged of interest for our analyses: three RCTs, one prospective observational study and three retrospective chart review studies.

Of the RCTs, the most recent was a "three-arm" trial enrolling 3026 patients (per-protocol population) divided in amiodarone ($n = 974$), lidocaine ($n = 993$) or placebo ($n = 1059$).[6] Such trial was by far the largest trial since the other two comparing amiodarone with lidocaine[22] or with placebo[23] included only a total of 347 and 304 patients, respectively.

The only prospective observational study that compared lidocaine vs no lidocaine in OOH-CA patients and included 116 patients and was over 25 years old[24]; the three retrospective studies included 290 (lidocaine vs no lidocaine),[25] 180 (amiodarone vs no amiodarone)[14] and 118 patients (amiodarone vs lidocaine).[15] Only the latter study was performed in patients suffering from in-hospital CA.