The Use of Antiarrhythmic Drugs for Adult Cardiac Arrest: A Systematic Review

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ABSTRACT

Aims

In adult cardiac arrest, antiarrhythmic drugs are frequently utilized in acute management and legions of medical providers have memorized the dosage and timing of administration. However, data supporting their use is limited and is the focus of this comprehensive review.

Methods

Databases including PubMed, Cochrane Library (including Cochrane database for systematic reviews and Cochrane Central Register of Controlled Trials), Embase, and AHA EndNote Master Library were systematically searched. Further references were gathered from cross-references from articles and reviews as well as forward search using SCOPUS and Google scholar. The inclusion criteria for this review included human studies of adult cardiac arrest and anti-arrhythmic agents, peer-review. Excluded were review articles, case series and case reports.

Results

Of 185 articles found, only 25 studies met the inclusion criteria for further review. Of these, 9 were randomised controlled trials. Nearly all trials solely evaluated Ventricular Tachycardia (VT) and Ventricular Fibrillation (VF), and excluded Pulseless Electrical Activity (PEA) and asystole. In VT/VF patients, amiodarone improved survival to hospital admission, but not to hospital discharge when compared to lidocaine in two randomized controlled trials.

Conclusion

Amiodarone may be considered for those who have refractory VT/VF, defined as VT/VF not terminated by defibrillation, or VT/VF recurrence in out of hospital cardiac arrest or in-hospital cardiac arrest. There is inadequate evidence to support or refute the use of lidocaine and other antiarrythmic agents in the same settings.

Keywords:

“heart arrest”, “cardiopulmonary resuscitation” , “cardiac arrest” , “Anti-Arrhythmia Agents” , “Lidocaine” , “procainamide” , “amiodarone” , “bretylium” , “magnesium”

INTRODUCTION

In the chain of survival concept[1, 2] provision of early access, early cardio-pulmonary resuscitation (CPR), early defibrillation and early advanced life, support, including intravenous drugs, should improve survival in sudden cardiac arrest. Survival rates for prehospital cardiac arrest vary in published reports from 2% to over 20%.[3, 4]

Intravenous antiarrhythmic drugs are routinely use as part of advanced care in both prehospital or in-hospital cardiac arrest, and the memorization of not only which drugs, but doses and when they should be administered is a memorable aspect of ACLS teaching and courses. However there have been relatively few formal evaluations of whether antiarrhythmic drugs (such as lidocaine, procainamide, amiodarone, bretylium, magnesium), improve clinical outcomes such as return of spontaneous circulation (ROSC), survival to discharge or survival with intact neurological function.

The current International Liaison Committee on Resuscitation (ILCOR) Advanced Cardiac Life Support Guidelines (2005)[5] acknowledged that there is currently very little or no placebo-controlled evidence for most antiarrhythmic drugs in cardiac arrest. However, despite this lack of evidence, our subjective experience of current clinical practice is the continued use of antiarrhythmic drugs on a routine basis. Indeed, the use of antiarrhythmic drugs appears ingrained in clinical practice in North America, Europe, as well as the developing world. We speculate that it would likely be difficult to conduct randomized/placebo controlled trials of antiarrhythmic drugs in cardiac arrest, due to physician attitudes, as well as difficulty with getting ethics approval and informed consent issues.

The aim of this paper was to conduct a systematic review of the published literature on the use of antiarrhythmic drugs (lidocaine, procainamide, amiodarone, bretylium, magnesium) in adult cardiac arrest (asystole, pulseless electrical activity, pulseless Ventricular Tachycardia (VT) and Ventricular Fibrillation (VF)).

METHODS

The review was conducted in accordance with the International Liaison Committee on Resuscitation (ILCOR) 2010 evidence evaluation process[6]. Review of the search strategy and findings were conducted by the authors. This review sought to identify evidence to address the question:[7] "In adult cardiac arrest (asystole, pulseless electrical activity, pulseless VT and VF) (prehospital [OHCA], in-hospital [IHCA]), does the use of antiarrhythmic drugs (lidocaine, procainamide, amiodarone, bretylium, magnesium) or combination with other drugs compared with not using drugs (or a standard drug regimen (without antiarrhythmics)) , improve outcomes (eg. ROSC, survival)"?

Two different search strategies were pursued, both targeting the same population: cardiac arrest, heart arrest, cardiopulmonary, resuscitation, post-cardiac arrest, and postresuscitation (textword and MeSH headings when applicable). These were the search strategies adopted by 2 independent reviewers for the paper, in a comprehensive and complementary review process. The combined results are presented. All duplicates were removed (no double counting).

As for the intervention, the first search strategy focused on the keywords arrhythmia, anti-arrhythmic, and unstable (MeSH headings when applicable), while the second search strategy looked at prophylactic use of single antiarrhythmic agents.

Databases were searched up to 4 Feb 2010, with PubMed, the Cochrane Library (including Cochrane database for systematic reviews and Cochrane Central Register of Controlled Trials), Embase, and the American Heart Association (AHA) Resuscitation Endnote Master library, which contains over 15,000 cardiac arrest related references. Moreover, cross-references from articles and reviews were forward searched using SCOPUS and Google scholar.

Search strategy #1 focused on the search terms "Heart Arrest" OR “cardiac arrest” OR “cardiopulmonary resuscitation” OR "Resuscitation" AND “Arrhythmia” OR “Anti-

Arrhythmic" OR "Anti-Arrhythmia Agents" OR "Unstable" AND "Post-Cardiac Arrest" OR "postresuscitation".

Search strategy #2 focused on the search terms "Amiodarone" OR "Lidocaine" OR "Lignocaine" OR "Procainamide" OR "Magnesium Sulfate" OR "Magnesium" OR "Bretylium" OR "Diltiazem" OR "Verapamil" OR "Digoxin" OR "Flecainide" OR "Propafenone" OR "Sotalol" OR "esmolol" OR "Atenolol" OR "Metoprolol" AND "prophylactic" OR "Post-Cardiac Arrest" OR "postresuscitation" AND "Resuscitation" OR "Cardiopulmonary Resuscitation" OR "Heart Arrest" OR "cardiac arrest".

In addition, we also searched for articles which cited: "Dorian P, et al. Amiodarone as compared with lidocaine for shock resistant ventricular fibrillation. NEJM 2002; 346: 884-90"[8] or "Kudenchuk P, et al. Amiodarone for resuscitation after out of hospital cardiac arrest due to ventricular fibrillation. NEJM. 1999; 342: 871-878".[9]

Inclusion criteria were human studies of adult cardiac arrest and anti-arrhythmic agents which were peer-reviewed. Exclusion criteria were review articles, case reports and case series. The articles were reviewed for relevance independently by two reviewers (MEHO/ML). Both titles and abstracts were reviewed, followed by the articles if suitable for review. Articles where the content was clearly unrelated were discarded. The abstracts of remaining articles were then reviewed and relevant studies identified for detailed review of the full manuscript. Where disagreement existed between reviewers, articles were included for detailed review. Finally, the reference lists of narrative reviews were examined to identify any additional articles not captured by the main search strategy.

Evidence appraisal

Studies were reviewed in detail and classified by level of evidence (LOE) (Table 1) and quality (rated poor, fair or good) according to agreed definitions (Table 2). "Methodological quality" (internal validity) of a study was defined as "the extent to which a study's design, conduct, and analysis has minimized selection, measurement, and confounding biases".[6] That quality is separate to "non-methodological" quality, which refers to the external validity or generalizability of the study results to other (broader) population groups.

Studies were allocated a rating for methodological quality (Good, Fair or Poor) according to the presence of the quality items for that Level of Evidence (see table 2): Good studies had most/all of the relevant quality items, Fair studies had some of the relevant quality items and Poor studies had few of the relevant quality items (but sufficient value to include for further review).

RESULTS

Of 185 articles found, only 25 studies met inclusion criteria for further review. Of these 11 were randomised controlled trials (RCT), Level of Evidence (LOE) 1, 7 were studies with concurrent controls (LOE 2), 2 were studies using retrospective controls (LOE 3), 2 were without controls (LOE 4) and 6 were not directly related to the specific patient/population (LOE 5) (see Table 3).

Nearly all of the studies report interventions for VF and pulseless VT rather than for asystole or PEA. Only one study[10] included patients in asystole or PEA. Evidence from Randomised Controlled Trials (RCT) is quite limited, and most of the studies use another antiarrhythmic drug as a control, rather than a placebo or no treatment. Thus, conclusions are limited to the relative effectiveness of antiarrhythmic drugs.

Studies looking at the use of Amiodarone in adult cardiac arrest:

Evidence from two randomized double-blind controlled studies[9] [8] (LOE1, Good Quality) demonstrated improved survival to hospital admission with amiodarone (compared to lidocaine) for patients in refractory VT/VF in the out-of-hospital setting. However there was no improvement in overall survival or survival with intact neurological function.

An additional randomized double-blind controlled trial[11] (LOE5 because population was not in cardiac arrest but in sustained VT, Fair Quality) demonstrated improved termination of VT and improved 24 hr survival with amiodarone (compared to lidocaine) for patients in VT, in the in-hospital setting.

Other lower LOE data on amiodarone were generally neutral[12] (LOE5, Fair Quality) found that amiodarone prevented recurrent hypotensive VT in 40% of individuals who had failed procainamide, lidocaine and bretylium. In in-hospital VT/VF arrests two studies[13], [14] (one LOE4, Fair Quality) and (one LOE2, Fair Quality) demonstrated no difference in

survival between patients given amiodarone or lidocaine.

Studies looking at the use of Lidocaine in adult cardiac arrest:

With lidocaine, evidence from a non-randomised prospective trial which compared patients treated with physicians on board ambulances versus those without, One study[15] (LOE2, Poor Quality); showed improved survival to discharge, with lidocaine and epinephrine (compared to epinephrine alone) for patients in VF, in the out-of-hospital setting. A retrospective review[16] (LOE2, Fair Quality); demonstrated improved survival to admission, with lidocaine (compared to standard treatment) for patients in VF, in the out-of-hospital setting. However, this study was also confounded by the inherent bias in that only ambulances with physicians on board could the patients be given lidocaine.

Two historical control OHCA studies,[17 18] (LOE3, Fair Quality) and an inhospital retrospective review,[19] (LOE2, Fair Quality); suggested decreased survival to admission with lidocaine (compared with sodium bicarbonate, nifekalant or standard treatment respectively) for patients in VF.

Lidocaine was also inferior to amiodarone in 2 studies,[8] (one LOE1, Good Quality), and one (LOE5, Fair Quality)[11], showing decreased survival to admission and 1 hour respectively, for patients in VF and VT respectively, in the in-hospital and out-of-hospital setting respectively.

Studies looking at the use of Magnesium in adult cardiac arrest:

Magnesium underwent 3 randomised placebo controlled trials, including one (LOE1, Good Quality)[20], and two (LOE1, Fair Quality)[21 22], and none demonstrated any increase in ROSC, for patients in VF, in the prehospital, Intensive Care Unit and Emergency Department setting respectively.

Studies looking at the use of Procainamide in adult cardiac arrest:

Evidence from a randomized prospective trial[23] (LOE5, Fair Quality), found procainamide (compared to lidocaine) improved termination of spontaneously occurring monomorphic VT in the in-hospital setting. Another retrospective review,[24] (LOE2, Fair Quality), found procainamide was associated with increased survival to 1h in patients with VF in an in-hospital setting.

However another retrospective review [25] (LOE4, Fair Quality), found procainamide and quinidine were associated with decreased survival in patients with VF in an out-of-hospital setting.

Studies looking at the use of Bretylium in adult cardiac arrest:

With Bretylium, evidence from 1 randomized double-blind controlled study[10] (LOE1, Fair Quality), found improved survival to admission with bretylium (compared to placebo) for patients with VF or asystole in the ED setting. Another 2 randomised out-of-hospital cardiac arrest (OHCA) trials[26 27] (LOE1, Good Quality) showed no difference in bretylium treated patients compared to those given lidocaine.

DISCUSSION

Despite the perceived necessity of antiarrhythmic drugs for patients with cardiac arrest due to VT or VF, there is actually little supporting evidence. Most of the studies were neutral or only demonstrated survival to admission, not to discharge. And in fact, most of the studies compared one drug to another; there were very few placebo controlled trials. Based on retrospective data and animal data lidocaine had been the standard of care for patients with cardiac arrest[16, 28]. In 2005, based on two randomized controlled trials (RCT) comparing amiodarone to lidocaine the standard of care changed to amiodarone.[8, 9] While we note that these trials were before the use of therapeutic hypothermia for OHCA due to VF, we observe that in these landmark trials there was solely an improvement in survival to hospital admission, but no difference in survival to discharge or neurological survival.

These trials were performed before the benefits of hypothermia was known, thus they did not incorporate this now proven therapy which improves survival after return of spontaneous circulation (ROSC). Whether survival to hospital discharge and neurologic survival could be improved with amiodarone and subsequent hypothermia is not known. If that is the case then a stronger argument for amiodarone could be made; if that is not the case then an argument could be made to not give an anti-arrhythmic drug at all. In addition, there may be obstacles of ethics as well as logic to a randomised controlled trial of a cardiac (rhythm) suppressant drug in asystolic cardiac arrest, where the focus is on trying to generate a rhythm with an output, not suppress it. Likewise, there are difficulties in a trial for PEA cardiac arrest, where rhythm abnormality is not the problem being treated.

With lidocaine which has been the standard of care for years, the evidence was mixed and most of the data were from trials with LOE 3 or lower. Positive studies included a non-randomised prospective trial[15] and a retrospective review.[16] However, 2 historical control out-of-hospital studies[17 18] and an inhospital retrospective review[19], suggested

decreased survival to admission with lidocaine (compared with bicarbonate, nifekalant or standard treatment respectively) for patients in VF. Lidocaine was also inferior to amiodarone in the 2 RCT mentioned above.[8 11] Similarly, there was no strong evidence for procainamide or magnesium.

With bretylium, evidence from 1 randomized double-blind controlled study, found improved survival to admission with bretylium (compared to placebo) for patients with VF or asystole in the ED setting. [10] Another 2 randomised OHCA trials, [26,27] showed no benefit when compared to lidocaine. The authors suggest that further investigation may be warranted into the role of bretylium in cardiac arrest as it is one of the few agents which have shown a benefit when compared to placebo. Unfortunately, as far as we are aware, manufacture of bretylium has been discontinued worldwide.

CONCLUSION

There is no conclusive evidence that anti-arrhythmic agents improve survival in cardiac arrest victims. While some agents have shown an improved survival to hospital admission, none have shown an improved survival to discharge or to an improved neurological survival. And most studies are tainted by the issue of comparing one anti-arrhythmic agent verses another. While we are waiting for more data it is reasonable to administer amiodarone in cardiac arrest victims with the hope that as our post arrest treatment improves the overall survival will ultimately improve.

DISCLAIMER

This review includes information on resuscitation questions developed through the C2010 Consensus on Science and Treatment Recommendations process, managed by the International Liaison Committee on Resuscitation (http://www.americanheart .org/ILCOR). The questions were developed by ILCOR Task Forces, using strict conflict of interest guidelines. In general, each question was assigned to two experts to complete a detailed structured review of the literature, and complete a detailed worksheet. Worksheets are discussed at ILCOR meetings to reach consensus and are published as the 2010 Consensus on Science and Treatment Recommendations (CoSTR). The conclusions published in the final CoSTR consensus document[29] may differ from the conclusions of in this review because the CoSTR consensus will reflect input from other worksheet authors and discussants at the conference, and will take into consideration implementation and feasibility issues as well as new relevant research.

CONFLICT OF INTEREST STATEMENT

All authors declare that there are no financial and personal relationships with other people or organizations that could inappropriately influence their work.

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Table 1. International Liason Committee on Resuscitation (ILCOR) 2010 Levels of Evidence for Studies of Therapeutic Interventions

LOE 1: Randomised Controlled Trials (or meta-analyses of RCTs)
LOE 2: Studies using concurrent controls without true randomisation (eg. “pseudo”-randomised)
LOE 3: Studies using retrospective controls
LOE 4: Studies without a control group (eg. case series)
LOE 5: Studies not directly related to the specific patient/population (eg. different patient/population, animal models, mechanical models etc.)

Notes for table 1:

LOE 1
Randomised Controlled Trials:
These studies prospectively collect data, and randomly allocate the patients to intervention or control groups.
LOE 2
Studies using concurrent controls without true randomisation:
These studies can be:
experimental - having patients that are allocated to intervention or control groups concurrently, but in a non-random fashion (including pseudo-randomisation: eg. alternate days, day of week etc), or
observational – including cohort and case control studies
A meta-analysis of these types of studies is also allocated a LOE = 2.
LOE 3
Studies using retrospective controls:
These studies use control patients that have been selected from a previous period in time to the intervention group.
LOE 4
Case series:
A single group of people exposed to the intervention (factor under study), but without a control group.
LOE 5
As with other categories of Levels of Evidence, we have used LOE 5 to refer to studies that are not directly related to the specific patient/population. These could be different patients/population, or animal models, and could include high quality studies (including RCTs).

Table 2. Quality assessment for studies assessing interventions

LOE 1	**Quality assessment for Randomised Controlled Trials** The seven factors included as the relevant quality items for RCTs are: • Was the assignment of patients to treatment randomised? • Was the randomisation list concealed? • Were all patients who entered the trial accounted for at its conclusion? • Were the patients analysed in the groups to which they were randomised? • Were patients and clinicians "blinded" to which treatment was being received? • Aside from the experimental treatment, were the groups treated equally? • Were the groups similar at the start of the trial? **Quality assessment for meta-analyses of RCTs** The six factors included as the relevant quality items for meta-analyses are: • Were specific objectives of the review stated (based on a specific clinical question in which patient, intervention, comparator, outcome (PICO) were specified) • Was study design defined? • Were selection criteria stated for studies to be included (based on trial design and methodological quality)? • Were inclusive searches undertaken (using appropriately crafted search strategies)? • Were characteristics and methodological quality of each trial identified? • Were selection criteria applied and a log of excluded studies with reasons for exclusion reported?
LOE 2	**Quality assessment for studies using concurrent controls without true randomisation** The four factors included as the relevant quality items for these studies are: • Were comparison groups clearly defined? • Were outcomes measured in the same (preferably blinded), objective way in both groups? • Were known confounders identified and appropriately controlled for? • Was follow-up of patients sufficiently long and complete? **Quality assessment for meta-analyses of studies using concurrent controls without true randomisation** The six factors included as the relevant quality items for meta-analyses are: • Were specific objectives of the review stated (based on a specific clinical question in which patient, intervention, comparator, outcome (PICO) were specified) • Was study design defined? • Were selection criteria stated for studies to be included (based on trial design and methodological quality)? • Were inclusive searches undertaken (using appropriately crafted search strategies)? • Were characteristics and methodological quality of each trial identified? • Were selection criteria applied and a log of excluded studies with reasons for exclusion reported?
LOE 3	**Quality assessment for studies using retrospective controls:** The four factors included as the relevant quality items for these studies are: • Were comparison groups clearly defined? • Were outcomes measured in the same (preferably blinded), objective way in both groups? • Were known confounders identified and appropriately controlled for? • Was follow-up of patients sufficiently long and complete?
LOE 4	**Quality assessment for case series** The three factors included as the relevant quality items for these studies are: • Were outcomes measured in an objective way? • Were known confounders identified and appropriately controlled for? • Was follow-up of patients sufficiently long and complete?
LOE 5	**Quality assessment for studies that are not directly related to the specific patient/population** LOE 5 studies are those not directly related to the specific patient/population (eg. different patient/population, animal models, mechanical models etc.), and should have their methodological quality allocated to the methodology of the study. The relevant quality criteria here are: • Good = randomised controlled trials (equivalent of LOE 1) • Fair = studies without randomised controls (equivalent of LOE 2-3) • Poor = studies without controls (equivalent of LOE 4).

Table 3. Summary of Evidence

Level of evidence	1	2	3	4	5
Evidence Supporting Clinical Question					
Good	Dorian et al.[8] (amiodarone vs lidocaine) Kudenchuk et al.[9] (amiodarone vs lidocaine)				
Fair	Nowak et al.[10] (bretylium vs placebo)	Herlitz et al (2003).[28] (lidocaine vs no lidocaine) Herlitz et al (1997).[16] (lidocaine vs no lidocaine)			Gorgels et al.[23] (procainamide vs lidocaine) Somberg et al.[11] (amiodarone vs lidocaine)
Poor		Ohshige et al.[15] (lidocaine vs no lidocaine)			
Evidence Neutral to Clinical Question					
Good	Allegra et al.[20] (Magnesium vs placebo) Hassan et al.[30] (Magnesium vs placebo) Olson et al.[27] (bretylium vs lidocaine) Haynes et al.[26] (bretylium vs lidocaine) Kovoor et al.[31] (sotalol vs lignocaine)				
Fair	Thel et al.[21] (Magnesium vs placebo) Fatovich et al.[22] (Magnesium vs placebo) Weaver et al.[17] (Lidocaine vs epinephrine)	Pollak et al.[14] (amiodarone vs lidocaine) Rea et al.[13] (amiodarone vs lidocaine) Stiell et al.[24] (bretylium, lidocaine, procainamide)	Tahara et al.[18] (nifekalant vs lidocaine)	Skrifvars et al.[32] (amiodarone)	Kowey et al.[33] (amiodarone vs lidocaine) Levine et al.[12] (amiodarone)
Poor					
Evidence Opposing Clinical Question					
Good					
Fair		van Walraven et al.[19] (Lidocaine vs no lidocaine)	Weaver et al.[17] (Lidocaine vs no lidocaine)	Hallstrom et al.[25] (Quinidine, procainamide vs no antiarrhythmic)	Nademanee et al.[34] (amiodarone, procainamide, bretylium vs no antiarrhythmic) Tomlinson et al.[35] (amiodarone)
Poor					