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Comparison between amiodarone and lidocaine for ventricular fibrillation treatment during cardiopulmonary resuscitation: a systematic review

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ABSTRACT: Cardiac arrest is a condition in which the heart mechanical functioning is compromised and usually it is due an electrical dysfunction of the cardiac cells and this can result in disorganization of cardiac rhythm and even heart failure, a situation of medical emergency in which seconds can make the difference between life and death. In cardiac arrest, it's necessary to perform cardiopulmonary resuscitation (CPR) maneuver and, if there are shockable rhythms (such as ventricular fibrillation and pulseless ventricular tachycardia), defibrillation should be administered on the patient. Even if the cardiac rhythm is reestablished, the condition is still serious due to the risk of recurrent electrical alteration of the heart. With the intent of avoiding a new rhythmic alteration of the heart, it's ministered antiarrhythmic drugs, such as amiodarone or lidocaine. Even though the use of one of these drugs is recommended, there are no consensuses about which one has higher survival rate of patients or which has the highest rate of return of spontaneous circulation. Thus, this systematic review aims to clarify which one of these two drugs is more efficient at preventing new electrical alterations of patients post cardiorespiratory arrest.

Keywords: Cardiac arrest; Antiarrhythmic drugs; Amiodarone; Lidocaine; Patient survival rate.

RESUMO: A parada cardíaca é uma condição em que o funcionamento mecânico do coração é comprometido e usualmente é devida a uma disfunção elétrica das células cardíacas, que pode resultar na desorganização do ritmo cardíaco, até numa falência cardíaca, uma situação de emergência médica em que segundos podem fazer a diferença entre a vida e a morte. Na parada cardíaca, é necessário que se realizem manobras de reanimação cardiopulmonar (RCP) e, caso haja presença de ritmo chocável (como a fibrilação ventricular e taquicardia ventricular sem pulso), se administre a desfibrilação no paciente. Mesmo que o ritmo cardíaco seja restabelecido, a condição ainda é grave devido ao risco de retorno da alteração elétrica do coração. Com a intenção de evitar novas alterações rítmicas do coração, são administradas drogas antiarrítmicas, como amiodarona e lidocaína. Embora seja recomendado o uso de um desses fármacos, não há consenso sobre qual deles tem maior sobrevida de pacientes, ou qual tem maior taxa de retorno de circulação espontânea. Sendo assim, essa revisão sistemática busca elucidar qual dessas duas drogas é mais eficiente para evitar novas alterações elétricas em pacientes pós-parada cardiorrespiratória.

Descritores: Parada cardíaca; Drogas antiarrítmicas; Amiodarona; Lidocaína; Sobrevida de pacientes.

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INTRODUCTION

Improving the outcome of out-of-hospital cardiac arrest (OHCA) is still a major healthcare challenge, due to the high mortality rates associated to this condition. Annually, approximately 420 000 cases were reported In United States and 275 000 in Europe[1]. More important, the fatality rate is generally more than 95 percent[2].

Sudden cardiac arrest (SCA) is defined as a natural and unexpected collapse of presumed cardiac etiology[3]. There are several conditions that may lead to the heart to suddenly lose its pumping capacity. In spite of the cause, if not treated immediately and properly, death may result in a few minutes[4].

Ventricular fibrillation (VF) and pulseless ventricular tachycardia (pVT) are the most common cause of cardiac arrest, being responsible for approximately 85% of sudden cardiac deaths[5]. Both conditions are treated primarily by cardiopulmonary resuscitation (CPR)[6] and electrical defibrillation, and therefore, have better outcomes when compared to other causes of cardiac arrest that do not respond to this kind of procedure (for example, asystole)[7].

Patients who return to spontaneous circulation (ROSC) after CPR and defibrillation, however, may present recurrence of these malignant arrhythmias. Hence, antiarrhythmic drugs, such as amiodarone or lidocaine, are frequently administered during and immediately after VF/pVT to reverse these dysrhythmias and prevent their relapse[8].

Amiodarone is a class III antiarrhythmic drug, according to the Vaughan-Williams Classification. Its properties includes inhibiting potassium, sodium and calcium channels. It also has anti-adrenergic effects by blocking the alfa and beta receptors. Amiodarone is indicated in patients with VF/pVT, after unsuccessful defibrillation[9,10]. Lidocaine is a class I antiarrhythmic drug, with sodium channel blockade. It has been used in VF patients who are refractory to defibrillation[11,12].

In 2015, the International Liaison Committee on Resuscitation (ILCOR) issued a guideline that recommended preferentially the use of amiodarone as the first choice of treatment for adult patients with VF/pVT[2]. However, studies point that both lidocaine and amiodarone are equivalent at preventing the refractory VF/pVT[2,13].

Since no agreement is observed in recent medical literature, and new studies addressing this issue have been recently published, our goal in this systematic review was to evaluate different studies comparing both of these drugs to find out which one of them can be more efficient clinically.

METHODS

Data sources and search strategy

For this systematic review, three databases were researched: SciELO, LILACS and Pubmed. In our access in November, 2018, no article with the desirable terms were found in SCielo or LILACS, therefore, only PubMEd results were reported.

Our search was structured by the following terms: "amiodarone [MeSH Terms] AND lidocaine[MeSH Terms] AND (resuscitation[MeSH Terms] OR cardiac arrest[MeSH Terms] OR cpr[MeSH Terms])". Filters were applied for language (English) and species (human).

Eligibility criteria and study selection

Inclusion criteria were pre-specified according to the PICOS approach (Table 1). We excluded studies about pediatric cardiac arrest, reviews, editorials, comments and letters to editor (Figure 1).

Table 1. PICOS approach for selecting studies in the systematic search

Population	Adult patients in cardiac arrest with recurrent (restarting after successful termination) VF/pVT, including in- and out-of-hospital setting
Intervention	Administration of amiodarone
Comparison	Lidocaine, placebo, combination of amiodarone and lidocaine, no drugs administered
Outcomes	Survival to admission to the hospital, survival to hospital discharge, favorable neurologic function at discharge, survival at 24 hrs/1-year post cardiac arrest
Study design	Randomized clinical trials and retrospective studies

*VF: ventricular fibrillation/ pVT: pulseless ventricular tachycardia

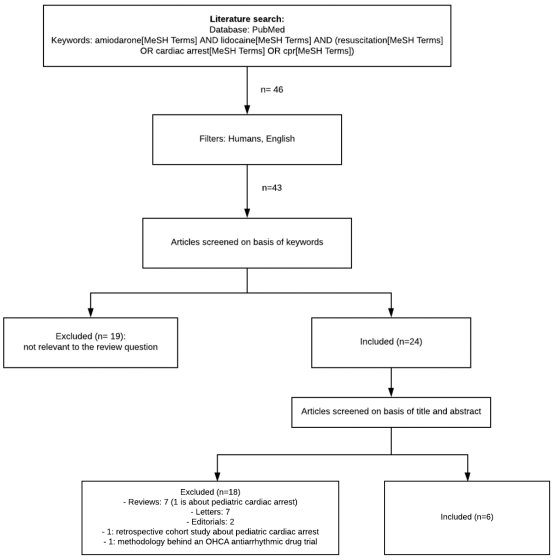

Figure 1. Flow diagram of included studies

Outcomes of interest

Endpoints of interest included survival to hospital admission, survival to hospital discharge, favorable neurologic status (modified Rankin score ≤3) at discharge, survival at 24 hrs/1-year post cardiac arrest, and adverse events.

RESULTS

The search identified 46 potentially relevant studies. As shown in the flow diagram (Figure 1), after applying filters and eliminating articles that did not meet the eligible criteria, six papers were selected for inclusion in the review: three randomized controlled trials (RCTs) and three retrospective medical record reviews. Initially, clinical trials and retrospective studies were analyzed separately. Table 2 and 3 present basic information of the included articles.

Table 2. Basic information of included clinical trials

Clinical Trial	Year	Author	Journal
Amiodarone as Compared with Lidocaine for Shock-Resistant Ventricular Fibrillation[2]	2002	Dorian et al.	N Engl J Med
Amiodarone, Lidocaine, or Placebo in Out-of-Hospital Cardiac Arrest[13]	2016	Kudenchuk et al.	N Engl J Med
Antiarrhythmic Drugs for Nonshockable-Turned-Shockable Out-of-Hospital Cardiac Arrest: The Amiodarone, Lidocaine or Placebo Study (ALPS)[14]	2017	Kudenchuk et al.	AHA Circulation

* N Engl J Med: The New England Journal of Medicine/ AHA: American Heart Association

Table 3. Basic information of included retrospective studies

Retrospective Study	Year	Author	Journal
Comparing intravenous amiodarone or lidocaine, or both, outcomes for inpatients with pulseless ventricular arrhythmias[15]	2006	Rea et al.	Crit Care Med
Amiodarone Compared with Lidocaine for Out-Of-Hospital Cardiac Arrest with Refractory Ventricular Fibrillation on Hospital Arrival: a Nationwide Database Study[7]	2016	Tagami et al.	Cardiovasc Drugs Ther
Acute hospital administration of amiodarone and/or lidocaine in shockable patients presenting with out-of-hospital cardiac arrest: a nationwide cohort study[16]	2016	Huang et al.	Int J Cardiol

Characteristics of included studies

a) Methods

All three clinical trials selected for the review were randomized and double-blind. The duration of the study published in 2002[5] was 5 years and 5 months and both studies conducted by Kudenchuk et al.[13,14] have the same duration (3 years, 5 months and 18 days) and setting.

The research led by Kudenchuk et al.[13,14] compared amiodarone, lidocaine and saline placebo after successful ROSC. Meanwhile, Dorian et al.[2] used a different experimental design; each kit given to paramedics contained either active amiodarone and lidocaine placebo or active lidocaine and amiodarone placebo. There was no saline placebo having its effect compared to antiarrhythmic drugs (Table 4).

Table 4. Clinical trials: study characteristics

Clinical Trial	Allocation	Blinding	Comparison between	Duration	Setting
Dorian et al., 2002	Randomized	Double-blind	Amiodarone and lidocaine	November 1995 - April 2001	Toronto EMS system, that follows treatment protocols in accordance with the AHA guidelines for ALCS
Kudenchuk et al., 2016	Randomized	Double-blind	Amiodarone, lidocaine and placebo	May 7, 2012 - October 25, 2015	55 EMS agencies across 10 North American sites participating in the ROC
Kudenchuk et al., 2017	Randomized	Double-blind	Amiodarone, lidocaine and placebo	May 7, 2012 - October 25, 2015	55 EMS agencies across 10 North American sites participating in the ROC

*EMS: emergency medical services/ ROC: Resuscitation Outcomes Consortium/ AHA: American Heart Association/ ACLS: advanced cardiac life support

We analyzed three retrospective studies, one from a multicenter study conducted in the USA[15], one from the Japanese Diagnosis Procedure Combination inpatient database[7] and one from the Taiwan's National Health Insurance Research Database (NHIRD)[16]. August 1, 2000, the start date for data collection of Rea et al.[15] study, is the date of the publication of the 2000 guidelines recommending amiodarone over lidocaine for VF/ pVT.

The retrospective studies compared routes of drug administration, drug dose and outcomes in patients receiving amiodarone or lidocaine or both or neither during the period of analysis (Table 5).

Table 5. Retrospective studies: article type, comparison and time interval covered by the studies

Retrospective study	Article type	Comparison between	Patients included if admitted between
Rea et al., 2006	Retrospective medical record review: comparative multicenter study (3 medical centers in the USA)	Amiodarone, lidocaine and combination of amiodarone and lidocaine	August 1, 2000 and August 1, 2002
Tagami et al., 2016	Nationwide database study: medical records from Japanese Diagnosis Procedure Combination inpatient database	Amiodarone and lidocaine	July 2007 and March 2013
Huang et al., 2016	Nationwide cohort study: medical records from Taiwan National Health Insurance Research Database (NHIRD)	Both (amiodarone and lidocaine), amiodarone (amiodarone only), lidocaine (lidocaine only), and neither	January 2004 and December 2011.

b) Participants

Table 6 and 7 summarizes the characteristics of participants of chosen clinical trials and retrospective studies, respectively. In all included studies[2,7,13,14,16], patients were eligible if they were adults with non-traumatic OHCA, except in the study of Rea et al.[15], that compared survival rates of in-hospital cardiac arrest treated with amiodarone or lidocaine or a combination of both. In the studies of Kudenchuk et al.[13,14], patients presenting with initial shock-refractory VF/VT were reported and analyzed in the research published in 2016[13]. The study published in 2017 also by Kudenchuk et al.[14], was an analysis in a separate cohort that initially had nonshockable OHCA and subsequently developed shock-refractory VF/VT.

The mean age of enrolled patients was over 60 years, and most patients were male.

Table 6. Clinical trials: patients

Clinical Trial	Eligible patients	N	Mean [±SD] age	Sex
Dorian et al., 2002	Non-traumatic OHCA VF resistant to 3 shocks, intravenous epinephrine, and a further shock; or recurrent VF after initially successful defibrillation	347	67±14 years	Male sex – 78%
Kudenchuk et al., 2016	Non-traumatic OHCA, shock-refractory VF or pVT after at least one shock, and with vascular access	3026	63.7±14.0 years (amiodarone) 63.0±14.7 years (lidocaine) 62.7±14.6 years (placebo)	Male sex – 80%
Kudenchuk et al., 2017	Nonshockable-turned-shockable non-traumatic OHCA: patients with initially nonshockable arrest rhythm that subsequently developed VF/VT refractory to ≥1 shock(s)	1063	64.5±16.5 years	Male sex – 70%

* OHCA: out-of-hospital cardiac arrest/ VF: ventricular fibrillation/ pVT: pulseless ventricular tachycardia/ Plus–minus values are means ±SD (standard deviation)

Table 7. Retrospective studies: patients

Retrospective Study	Eligible patients	N	Mean [±SD] age	Sex
Rea et al., 2006	IHCA secondary to VF/ pVT	194	62±14.0 years (amiodarone) 64.0±17 years (lidocaine) 65±12 years (combination)	Male sex – 72%
Tagami et al., 2016	Cardiogenic OHCA and refractory VF/ pVT	3951	68.4±15.1 years (amiodarone) 64.4±17.5 years (lidocaine)	Male sex – 75%
Huang et al., 2016	Non-traumatic OHCA undergoing DC shock and cardiopulmonary resuscitation during short emergency room stay (<6h)	27463	62.01 ± 15.76 years (both) 64.75 ± 16.18 years (amiodarone) 66.83 ± 16.28 years (lidocaine) 67.10 ± 17.19 years (neither)	Male sex – 67%

* IHCA: in-hospital cardiac arrest/ OHCA: out-of-hospital cardiac arrest/ VF: ventricular fibrillation/ pVT: pulseless ventricular tachycardia/ DC: direct-current/ Plus–minus values are means ±SD (standard deviation)

c) Intervention

In order to better compare the intervention among the studies, we listed the CPR procedures performed in patients included in each study. Table 8 and 10 summarize event characteristics and CPR maneuvers in patients analyzed, respectively, by clinical trials and retrospective studies. Table 9 and 11 present information about routes of drug administration and drug dose, in clinical trials and retrospective studies.

In clinical trials[2,13,14], amiodarone and lidocaine groups did not differ significantly in treatment or procedure, except for the infused experimental drug.

Dorian et al.[2] also evaluated the effect of time between the dispatch of the paramedics and the administration of the study drug on the proportion of patients with improved outcome: among patients for whom the length of time was equal or less than the median time (24 minutes), a higher proportion of patients survived to hospital admission was detected.

Drug doses administered were the same in both studies by Kudenchuk et al.[13,14] (300 mg of amiodarone and 120 mg of lidocaine, as initial dose, if the estimated body weight was >45.4 kg) and similar doses were used in the other clinical trial evaluated..

In retrospective studies[7,15,16], there was a lack of information about the cardiac arrest event and the treatment they received before the administration of antiarrhythmic drugs.

In Rea et al.[15], the standard deviation values for antiarrhythmic drugs doses are high, except for the second dose of amiodarone, which is zero (150±0 mg; since one syringe of amiodarone contains 150 mg, for practical reasons, more commonly the patient in an emergent situation may be given 150 mg. Difficulties in preparing and administering amiodarone have been reported during cardiac arrest). Tagami et al.[7] did not provide drug doses.

Table 8. Clinical trials: cardiac arrest and resuscitation

Clinical Trial	Time from dispatch to arrival of paramedics	Time from dispatch to first dose of trial drug	Compression/Defibrillation/Ventilation
Dorian et al., 2002	7±3 minutes	25±8 minutes	CPR by bystander (27%), procedures performed by paramedics (shock and intubation)
Kudenchuk et al., 2016	5.8±2.6 min (amiodarone) 5.6±2.4 min (lidocaine) 5.8±2.6 min (placebo)	19.3±7.4 minutes	CPR by bystander (56%), PAD shock by bystander (5,6%), procedures performed by paramedics (advanced airway management, shocks, compressions)
Kudenchuk et al., 2017	6.1±2.8 minutes	26.9±8.9 minutes	CPR by bystander (46%), procedures performed by paramedics (advanced airway management, shocks, compressions)

* CPR: cardiopulmonary resuscitation/ PAD: public access defibrillator/ Plus–minus values are means ±SD (standard deviation)

Table 9. Clinical trials: antiarrhythmic drugs

Clinical Trial	Amiodarone: routes of drug administration and drug dose	Lidocaine: routes of drug administration and drug dose	Placebo
Dorian et al., 2002	- Intravenous - 5 mg per kilogram of estimated body weight - If VF persisted after a further shock, second dose was administered (2.5 mg per kg).	- Intravenous - 1.5 mg per kilogram at a concentration of 10 mg per mL - If VF persisted after a further shock, second dose was administered (1.5 mg per kg).	-
Kudenchuk et al., 2016	- Intravenous or intraosseous - Initial dose: 2 syringes (1 syringe if the estimated body weight was <45.4 kg). Each syringe contained 150 mg of amiodarone. - If VF persisted after a further shock, a supplemental dose (one syringe) was administered.	- Intravenous or intraosseous - Initial dose: 2 syringes (1 syringe if the estimated body weight was <45.4 kg). Each syringe contained 60 mg of lidocaine. - If VF persisted after a further shock, a supplemental dose (one syringe) was administered.	Saline placebo
Kudenchuk et al., 2017	- Intravenous or intraosseous - Initial dose: 2 syringes (1 syringe if the estimated body weight was <45 kg). Each syringe contained 150 mg of amiodarone. - If VF persisted after a further shock, a supplemental dose (one syringe) was administered.	- Intravenous or intraosseous - Initial dose: 2 syringes (1 syringe if the estimated body weight was <45 kg). Each syringe contained 60 mg of lidocaine. - If VF persisted after a further shock, a supplemental dose (one syringe) was administered.	Saline placebo

*VF: ventricular fibrillation

Table 10. Retrospective studies: cardiac arrest and resuscitation

Retrospective Study	Time to initiation of CPR	Time from dispatch to first dose of trial drug	Compression/Defibrillation/ Ventilation
Rea et al., 2006	1±2 min (amiodarone) 2±4 min (lidocaine) 22s±1 min (combination)	14±9 min (amiodarone) 6±5 min (lidocaine) 9±8 min (combination)	ACLS interventions at time of event: -Intubation/ mechanical ventilation: 50% -Defibrillator: 1.5%
Tagami et al., 2016	Not available in the article	Not available in the article	EMS resuscitation procedures follow the Japanese guidelines for CPR
Huang et al., 2016	Not available in the article	Not available in the article	Rate of bystander CPR was 31.4% in Taiwan/ Compressions, DC shocks, tracheal intubation

* CPR: cardiopulmonary resuscitation/ ACLS: advanced cardiovascular life support/ EMS: emergency medical services/ DC: direct-current/ Plus–minus values are means ±SD (standard deviation)

Table 11. Retrospective studies: antiarrhythmic drugs

Retrospective Study	Amiodarone: routes of drug administration and drug dose	Lidocaine: routes of drug administration and drug dose	Combination of amiodarone and lidocaine
Rea et al, 2006	- Intravenous - First dose: 190±68.9 mg - Second dose if VF persisted after a further shock: 150±0 mg	- Intravenous - First dose: 96.2±22 mg - Second dose if VF persisted after a further shock: 78.7±31.8 mg	- Intravenous
Tagami et al, 2016	- Intravenous - Drug dose: not available in the article	- Intravenous - Drug dose: not available in the article	-
Huang et al, 2016	- Intravenous - First dose: 300 mg - Second dose if VF persisted after a further shock: 150 mg	- Intravenous - First dose: 1.0-1.5 mg per kilogram - Second dose if VF persisted after a further shock: 0.5-0.75 mg per kg	- Intravenous

*VF: ventricular fibrillation/ Plus–minus values are means ±SD (standard deviation)

d) Outcomes

Survival to hospital discharge was assessed in all studies[2,7,13-16] either as a primary or secondary outcome depending on the study.

The studies by Kudenchuk et al.[13,14] included favorable neurologic function at discharge as a secondary endpoint. It was defined as a score on the modified Rankin scale (ranging from 0, no symptoms, to 6, death) of 3 or less, indicating the ability to conduct activities of daily living independently or with minimal assistance.

Adverse drug-related effects were analyzed by Dorian et al.[2] and Kudenchuck et al.[14]. In Dorian et al.[2], adverse events were defined as the need to administer atropine (treatment for bradycardia) or dopamine (pressor treatment) after administration of the study drug. In the latest trial by Kudenchuk et al.[14], these effects were defined as those previously reported with these medications that occurred within 24 hours of their administration, including anaphylaxis, thrombophlebitis requiring treatment, clinical seizures, and bradycardia requiring temporary cardiac pacing.

In Huang et al.[16], patients were followed for 1 year after the day of event or until loss to follow-up or death.

Table 12. Clinical trials: outcomes

Clinical Trial	Outcome
Dorian et al., 2002	1. Survival to admission to the hospital ICU 2. Survival to hospital discharge and adverse events
Kudenchuk et al., 2016	1. Survival to hospital discharge 2. Favorable neurologic function at discharge
Kudenchuk et al., 2017	1. Survival to hospital discharge 2. Favorable neurologic function at discharge and adverse events

* ICU: intensive care unit

Table 13. Retrospective studies: outcomes

Retrospective Study	Outcome
Rea et al., 2006	1. Survival at 24 hrs post–cardiac arrest 2. Survival to hospital discharge
Tagami et al., 2016	1. Survival to hospital discharge
Huang et al., 2016	1. Survival at 1-year post–cardiac arrest 2. Survival to admission to the hospital ICU and survival to hospital discharge

* ICU: intensive care unit

Results of Individual Studies

The results of included clinical trials are summarized in Table 12. Table 13 contains the results of retrospectives studies.

Table 14. Clinical trials: results

Clinical Trial	Primary outcome	Secondary outcome
Dorian et al., 2002	1. Survival to admission to the hospital ICU =Amiodarone (180 patients total): 41 (22.8%) Lidocaine (167 patients total): 20 (12%)	2a. Survival to hospital discharge = 21% of patients who survived to hospital admission after receiving amiodarone and 25% of patients who survived to hospital admission after receiving lidocaine survived to hospital discharge 2b. Adverse events (need to administer atropine or dopamine after administration of the study drug) = 24% and 23% of patients treated, respectively, with amiodarone and lidocaine needed treatment of bradycardia with atropine, and 7% and 4% of patients treated, respectively, with amiodarone and lidocaine needed pressor treatment with dopamine
Kudenchuk et al., 2016	1. Survival to hospital discharge = Amiodarone (974 total patients): 237 (24.4%) Lidocaine (993 total patients): 233 (23.7%) Placebo (1059 total patients): 222 (21%)	2. Favorable neurologic function at discharge (modified Rankin score ≤3) = Amiodarone: 18.8% Lidocaine: 17.5% Placebo: 16.6%
Kudenchuk et al., 2017	1. Survival to hospital discharge = Amiodarone (389 total patients): 16 (4.1%) Lidocaine (358 total patients): 11 (3.1%) Placebo (316 total patients): 6 (1.9%)	2. Favorable neurologic function at discharge (modified Rankin score ≤3) = Amiodarone: 2.1% Lidocaine: 1.7%, Placebo: 1%

* ICU: intensive care unit

Table 15. Retrospective studies: results

Retrospective Study	Primary outcome	Secondary outcome
Rea et al., 2006	1. Survival at 24 hrs post–cardiac arrest = Both (only 34 patients out of 41 were available): 17 (50%) Amiodarone (only 62 out of 74 were available): 34 (55%) Lidocaine (only 68 out of 79 were available): 43 (63%)	2. Survival to hospital discharge = Both (41 patients): 42% Amiodarone (74): 39% Lidocaine (79): 45%
Tagami et al., 2016	1. Survival to hospital discharge = Amiodarone (1743 total patients): 281 (16.1%) Lidocaine (2208 total patients): 389 (17.6%)	-
Huang et al., 2016	1. Survival at 1-year post–cardiac arrest = Both (1487 total patients): 165 (11.10%) Amiodarone (6459 total patients): 534 (8.27%) Lidocaine (1077 total patients): 77 (7.15%) Neither (18440 total patients): 602 (3.26%)	2a. Survival to admission to the hospital ICU = Both: 34.10% Amiodarone: 27.17% Lidocaine: 25.53% Neither: 15.48% 2b.Survival to hospital discharge = Both: 12.25% Amiodarone: 9.54% Lidocaine: 8.36% Neither: 3.31%

Table 16 - Adjusted analysis on survival to hospital discharge

	Dorian et al., 2002	Kudenchuk et al., 2016	Kudenchuk et al., 2017
1. Amiodarone vs. Placebo	Not available in the article	3,2% (difference in survival)	2,5% (difference in survival)
-CI (95%)		(-0.4 to 7.0)	(-0.2 to 5.1)
-P value		0,08	0,07
2. Lidocaine vs. Placebo	Not available in the article	2,6% (difference in survival)	1,1% (difference in survival)
-CI (95%)		(-1.0 to 6.3)	(-1.3 to 3.4)
-P value		0,19	0,28
3. Amiodarone vs. Lidocaine	2,49 (Odds ratio for survival between drugs)	0,7% (difference in survival)	Not available in the article
-CI (95%)	(-1.0 to 4.85)	(-3.2 to 4.7)	
-P value	0,007	0,7	

DISCUSSION

In this systematic review, direct and indirect evidence from three RCTs and three retrospective studies were analyzed to compare the effectiveness of amiodarone and lidocaine administered to reverse VF/pVT and prevent their recurrence in adults with non-traumatic cardiac arrest.

Only one article affirmed the superiority of one drug over another in its outcome: Dorian et al.[2] stated that amiodarone leads to substantially higher rates of survival to hospital admission, as compared with lidocaine. Huang et al.[16] also evaluated the survival at hospital admission, and concluded that both medication did not differ significantly, although survival rates were improved with association of using drugs, as opposed to non-treatment.

Regarding survival at a hospital discharge: the studies suggest that there is no significant difference in the rate of survival between amiodarone and lidocaine[2,7,13-16]. In addition, research comparing antiarrhythmic drugs with placebo shows that neither amiodarone nor lidocaine resulted in a significantly higher rate of survival than the rate of placebo[13,14]. However, when comparing drugs with non-treatment, survival rates were higher in patients given medications[16].

Limitations

This systematic review has several limitations. The RCTs and the retrospective studies are not directly comparable: since retrospective studies consist of analyzing outcomes that have already occurred from events that were not controlled, the quality tends to be lower than that of randomized double-blind clinical trials. High standard deviation values for antiarrhythmic drugs doses in Rea et al.[15] show that there is no homogeneity in the doses administered, creating a variability inside the group of patients given amiodarone and inside the group given lidocaine. Even though the study acknowledges that despite existing recommended doses of Amiodarone or Lidocaine based on guidelines, not all of the patients received the suggested dosage. In contrast, two retrospective studies - Tagami et al.[7] and Huang et al.[16] - deal with a very large number of patients, which contribute to increase the quality of the studies, even though there are some information in this studies such as the time until drug administration or the dosage of drugs administered to patients that are not presented.

There are also differences in the emergency medical systems of the countries in which the studies were conducted: the included studies were performed in various countries, such as Canada[2], North America[13,14,15], Japan[7] and Taiwan[16]. In the study conducted in North America[13,14] patients were randomized at the scene by paramedics. Meanwhile, in Japan[7], drugs were provided only after hospital arrival because paramedics are not allowed to administer any antiarrhythmic drugs (neither amiodarone nor lidocaine) in pre-hospital settings. This could be responsible for differences of time from cardiac arrest to first administration of the antiarrhythmic drug between the studies[7].

Huang et al.[16] doesn't present how much time the patient was having a cardiac arrest before the arrival of paramedics and time until the administration of any drug. The article cites that amiodarone or lidocaine was administered within 20 minutes after the start of the clinical emergency. Moreover, there were no justifications on why the use of amiodarone simultaneously of lidocaine during the episodes of cardiac arrest

Rea et al.[15] retrospective study points that the mean of time until the first administration of Lidocaine was of 6 minutes, while the mean of Amiodarone was of 14 minutes and the mean of both drugs simultaneously was of 9 minutes. However, differently from the other articles this prospective study was realized within three academic medical centers in the United States, and the patients were already hospitalized and thus there was no significant time of cardiac arrest without medical assistance.

CONCLUSION

The data presented on the articles analyzed point to an inconclusive result. The only article to present a direct difference between both drugs is Dorian et al.[2] which states a better overall survival rate of patients that received amiodarone. However, all of the other articles[7,13-16] points to a non-existent difference between both drugs in overall survival rate of patients.

It's possible that the different countries, communities, time of cardiac arrest and other variables influenced the outcome of all the articles, including the one by Dorian et al.[2] and thus it's recommended the design of new RTCs similarly to Kudenchuk et al.[13,14] studies with the intent of reducing the number of variables that may influence or prevent the conclusion of which one of the drugs has higher patient survival rate.

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