TURKISH JOURNAL OF EMERGENCY MEDICINE

Original Article

Access this article online

Quick Response Code:

Website: www.turkjemergmed.org

DOI: 10.4103/2452-2473.301917

Efficacy of bicarbonate therapy for adults with cardiac arrest: A systematic review and meta-analysis of randomized-controlled trials

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Abstract:

OBJECTIVES: Because the benefits of bicarbonate therapy remain unclear, it is not routinely recommended for the cardiopulmonary resuscitation (CPR) given to individuals with cardiac arrest (CA). This study aims to evaluate the clinical benefits of bicarbonate therapy in adults with CA.

METHODS: Without any language restriction, we searched PubMed/MEDLINE, Scopus, Web of Science, and Cochrane CENTRAL from the inception until April 30, 2020. We performed hand-search to identify the relevant trials included in previous meta-analyses. Included studies were randomized controlled trials (RCTs) comparing bicarbonate and placebo treatment in adults with CA. Two authors independently assessed the trial risk of bias. The primary outcome was the survival to hospital admission. The secondary outcomes included the return of spontaneous circulation, the survival to hospital discharge, and the neurological outcome at discharge. We calculated the odds ratios of those outcomes using the Mantel-Haenszel model and assessed the heterogeneity using the I^2 statistic.

RESULTS: Our searches found 649 unduplicated studies. Of these, three RCTs involving 1344 patients were included in the meta-analysis. The trial risk of bias ranged between fair and poor, mainly due to no blindness of outcome assessment and the selective reports of outcomes. Bicarbonate therapy showed no significant improvement in the survival to hospital admission (odds ratio [OR] 0.96; 95% confidence interval [CI] 0.73–1.25). Subgroup analysis in those receiving prolonged CPR showed a similar result (OR 0.88; 95% CI 0.10–8.01). No study reported the predefined secondary outcomes.

CONCLUSION: For both acute and prolonged CPR, bicarbonate therapy might not show benefit to improve the rate of survival to hospital admission in adults with cardiac arrest.

Keywords:

Bicarbonate, cardiac arrest, meta-analysis, survival, systematic review

Submitted: 01-07-2020
Revised: 09-08-2020
Accepted: 04-09-2020
Published: 01-12-2020

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Introduction

Cardiac arrest (CA) is a common health problem that needs a life-saving intervention of cardiopulmonary resuscitation (CPR). CA also remains one of the most serious health conditions. Each year, CA claims around 3.7 million lives across the world.[1] In the United States, the annual incidence of CA ranged between 180,000 and 450,000 times, which accounts for 7%–18% of all deaths.[2] CPR is a complicated procedure with an effort to restart the cardiac function and restore normal circulation. Standard CPR involves both basic life support and advanced cardiac life support (ACLS).

How to cite this article: Wongtanasarasin W, Srisurapanont K. Efficacy of bicarbonate therapy for adults with cardiac arrest: A systematic review and meta-analysis of randomized-controlled trials. Turk J Emerg Med 2021;21:24-9.

Box-ED Section:

What is already known on the study topic?

Evidence of bicarbonate administration in adults with cardiac arrest remains unclear.

Despite stated in the ACLS guidelines that acidosis is one of the reversible causes of cardiac arrest, bicarbonate therapy is not routinely recommended.

What is the conflict on the issue? Has it importance for readers?

The efficacy of bicarbonate therapy given to adults with cardiac arrest were controversial.

In the past decades, some evidences suggested the use of bicarbonate in adults with cardiac arrest and suspected acidosis; however, the majority recommended against the use of it.

How is this study structured?

This was a systematic review and meta-analysis of randomized-control trial.

What does this study tell us?

For adults with cardiac arrest, the benefit of bicarbonate administration during either acute or prolonged (>15 minutes) CPR was unclear.

Bicarbonate therapy for CA remains controversial. According to the latest standard guideline for managing CA,[3] ACLS consists of defibrillation for a shockable cardiac rhythm and medication administration if indicated. Three medications recommended in the latest guideline of CA include adrenaline (epinephrine), amiodarone, and lidocaine.[4] Bicarbonate therapy for CA has been an issue of debate.[5] Two studies showed the positive outcomes with the use of bicarbonate.[6,7] However, the predominant evidences showed no benefit.[8-11] Early ACLS guidelines recommended the use of routine bicarbonate administration as part of the algorithm,[12] but recent guidelines, latest in 2018,[4] no longer recommended its use. The debate in the literature is continuing, but at the present moment, bicarbonate administration is only recommended for CA related to hyperkalemia or tricyclic antidepressant overdose (class IIb recommendation, level of evidence C).[13]

Thus, this study aimed to perform an up-to-date systematic review and meta-analysis to determine the efficacy of bicarbonate therapy for adults with CA.

Methods

This manuscript was prepared based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines for systematic reviews.[14] Two authors (WW/KS) independently conducted a comprehensive search on multiple bibliographic databases, including PubMed/MEDLINE, Scopus, Web of Science, and Cochrane CENTRAL. The searches covered the periods since their inceptions until April 30, 2020. No language restriction was applied. The Medical Subject Headings terms included a combination of search terms with various spelling and endings: "bicarbonate," "sodium bicarbonate," "lithium bicarbonate," "cardiac arrest," "heart arrest," "cardiopulmonary arrest," "cardiopulmonary resuscitation," "sudden death," and "sudden collapse". The references of all relevant meta-analyses were further screened to identify the additional trials. The regulatory website "clinicaltrials.gov" was also searched to identify any unpublished trial. Our review was prospectively registered with PROSPERO (CRD42020151624).

Eligible criteria and study selection

Included studies were randomized controlled trials (RCTs) comparing bicarbonate and placebo therapy in adults (≥18 years) with CA. Each included trial must report at least one of the following outcomes: Survival to hospital admission, the return of spontaneous circulation, survival to hospital discharge, and neurological outcome at discharge. We did not limit the sites of CA, and both out-of-hospital and in-hospital CA were included. Two authors (WW/KS) independently screened the search results to identify potentially eligible trials, and obviously unrelated articles were excluded. Full manuscripts of the potential trials were subsequently retrieved with eligibility independently assessed by two reviewers (WW/KS) against prespecified criteria and evaluated for inclusion [Figure 1]. At each step of selection, disagreements were discussed and resolved or referred to a third reviewer for the conclusion.

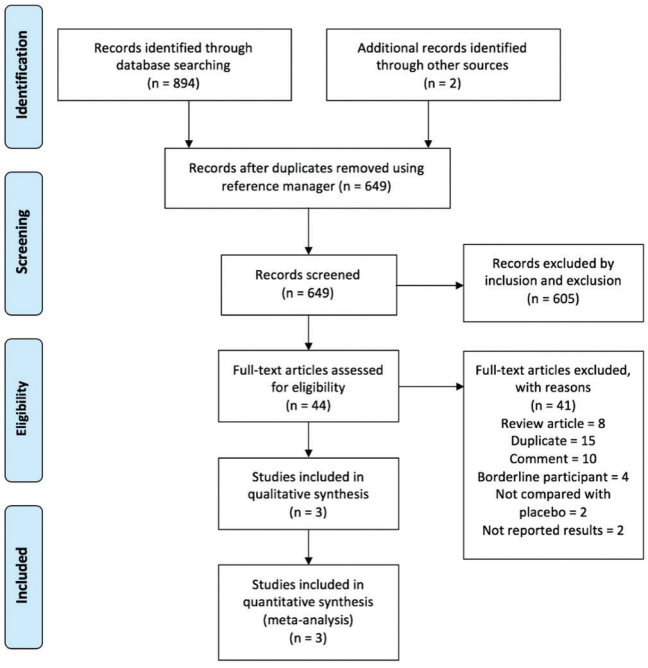

Figure 1: Flow diagram

Outcomes of interest

The primary outcome was the rate of survival to hospital admission. The secondary outcomes of interest were the rate of return of spontaneous circulation, the rate of survival to hospital discharge, and neurological outcome at discharge. Good neurological outcome was defined by the cerebral performance category score of 1–2. There is no universal definition of prolonged CPR, according to the Utstein standard reporting guidelines.[15,16] To determine the beneficial effects of bicarbonate therapy during prolonged CPR, we performed a subgroup analysis of outcomes reported after 15 min of resuscitation referred to the previously published studies.[9,17]

Assessment of trial risk of bias

Two assessors (WW/KS) independently evaluated the risk of bias of each trial using the modified version of the Cochrane collaboration's tool for assessing the risk of bias.[18,19] Three categories of the risks of bias were high, unclear, and low. The areas of bias being assessed included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias (including intention-to-treat analysis). Any discrepancies arisen were resolved by the third-party consensus.

Data synthesis and statistical analysis

Two authors (WW/KS) independently extracted the data on participant demographics, sample sizes, details of the intervention, protocols used, and reported outcomes using a standardized data collection form. We used the Review Manager version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark) to perform the statistical analysis.[20] We intended to calculate odds ratio (OR) with 95% confidence intervals (CIs) using the Mantel-Haenszel model because we presumed that identified studies were homogeneous. The statistical significance was defined as the $P < 0.05$. We assessed the heterogeneity of data using I^2 statistic. We performed the Egger's test for funnel plot asymmetry to determine the publication bias.

Results

Search strategies

From the PRISMA flow diagram [Figure 1], we retrieved 894 citations from the database as mentioned earlier searches and two relevant studies from hand searches. After removing the duplicates, 649 abstracts remained. Of these, 605 articles were excluded by abstract screening, and 41 articles were excluded after full-text assessment. Finally, only three trials were included in the meta-analysis.[8,9,21]

Characteristics and risk of bias of the included trials

The meta-analysis consisted of 1344 participants. All included trials were performed in high-income countries, one from South Korea, one from the United States, and the other from Norway [Table 1]. Participants' mean age was above 60 years old. About half of the CA s were witnessed, but the bystander CPR varies among the trials. The included studies were assessed using the Cochrane Risk of Bias Tool for RCTs.[18] Two and one trials had fair and poor risk of bias, respectively [Figure 2].

Survival to hospital admission of the whole cohort

Based on the homogenous data, the pooled ORs showed no significant improvement on the survival to hospital admission (OR = 0.96, 95% CI = 0.73–1.25, $I^2 = 0\%$) [Figure 3]. Moreover, due to limited number of included trials, the Egger's test could not be analyzed.

Survival to hospital admission after prolonged cardiopulmonary resuscitation

We performed a subgroup analysis of two studies reporting the outcome of prolonged CPR. The heterogeneous data showed no significant improvement of survival to hospital admission (OR = 0.88, 95% CI = 0.10–8.01, $I^2 = 71\%$) [Figure 4].

Discussion

Based on the consistent outcomes obtained from three

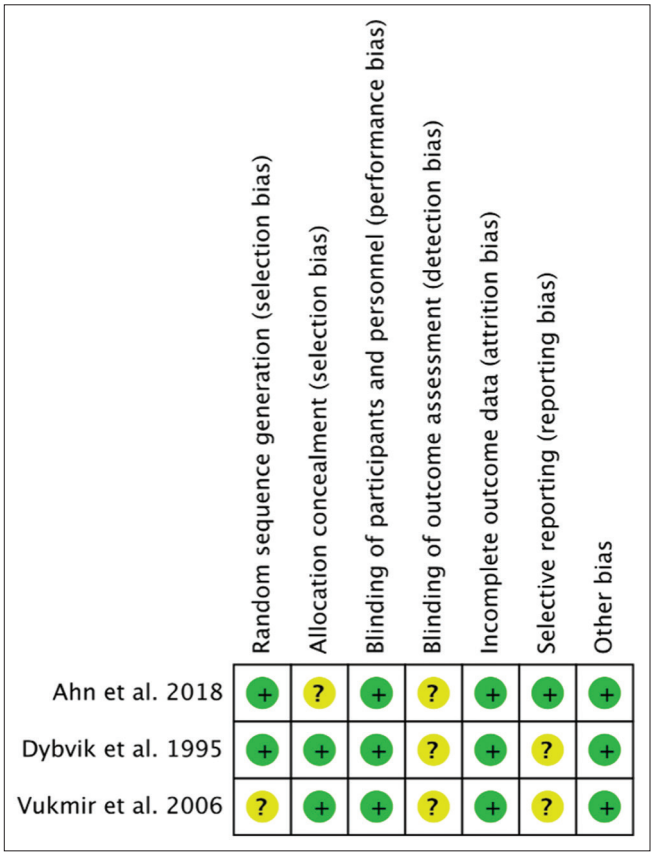

Figure 2: Risk of bias summary

Table 1: Characteristics of included trials

Study	Inclusion criteria	Participant	Interventions	Control	Management
Dybvik *et al.*, 1995	Inclusion criteria ≥16 years old Out-of-hospital cardiac arrest Persistent ventricular fibrillation after first defibrillation attempt or asystole Exclusion criteria Induced hypothermia Cardiac arrest of noncardiac origin	Oslo, Norway 65 years old Male: 76% VF: 44%, others: 56% Bystander CPR: 48%	Sodium bicarbonate 160 mmol/l, trometamol 300 mmol/l, disodium phosphate 20 mmol/l, and acetate 200 mmol/l	250 ml of 0.9% normal saline	Guidelines for cardiopulmonary resuscitation and emergency cardiac care 1992 Standards and Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiac Care 1986 European Resuscitation Council Guidelines for advanced life support 1992
Vukmir *et al.*, 2006	Inclusion criteria Cardiac arrest refractory to defibrillation Obtained intravenous access Exclusion criteria Suffering overt respiratory Traumatic origin cardiac arrest <18 years old Multiple failed attempts or without intravenous access Subgroup analysis time to advanced cardiac life support (≥15 min vs. <15 min)	Pittsburgh, Pennsylvania, USA 67.3 years old Male: - Initial rhythm: - Witnessed: 56% Bystander CPR: 17.1%	1 ampule (50 mEq/L) of bicarbonate early in the arrest cycle	Equal amount of normal saline	Standard advanced cardiac life support protocol including chest compressions, ventilation, defibrillation, epinephrine, atropine, antiarrhythmic drugs, and vasopressors if indicated
Ahn *et al.*, 2018	Inclusion criteria ≥18 years old Out-of-hospital cardiac arrest Nontraumatic origin Prolonged cardiopulmonary resuscitation Severe metabolic acidosis Exclusion criteria Do-not-resuscitate order Extracorporeal cardiopulmonary resuscitation Return of spontaneous circulation within 10 min of advanced cardiac life support No severe metabolic acidosis on after 10 min of cardiopulmonary resuscitation	64.5 years old Male 78% Seoul, Korea VF/pVT: 4%, PEA:12%, Asystole: 84% Witnessed: 56% Bystander CPR: 72%	50 mEq/L sodium bicarbonate 50 ml	Normal saline 50 ml	Standard ACLS including chest compression, intubation, ventilation, defibrillation, epinephrine and antiarrhythmic drugs if indicated

ACLS=Advanced cardiac life support, CPR=Cardiopulmonary resuscitation, PEA=Pulseless electrical activity, VF Ventricular fibrillation, pVT=Pulseless ventricular tachycardia

RCTs, bicarbonate therapy for adults with CA cannot improve the survival to hospital admission. The therapy also gives no benefit for those receiving prolonged CPR. The 2019 Utstein-style reporting templates were not applied,[15,16] which results in no report of other important outcomes after CPR, including the rates of return of spontaneous circulation, survival to hospital discharge, and neurological outcome at discharge. Moreover, qualities of the included studies were slightly low which resulted in inconcludable results.

To our knowledge, this is the first systematic review and meta-analysis of RCTs assessing the benefits of bicarbonate therapy for adults with CA. Bicarbonate therapy was routinely administered during the CPR taken place in the 1980s. However, this practice has been less common due to several reports of no beneficial effects and some unintentional harmful effects.[8,10,22-25] A previous literature review in this topic published in 2016 included a total of 16 studies. However, most of them were retrospective and observational studies. That review concluded that bicarbonate therapy demonstrated little benefit and might harm the patients.[5] The latest ACLS guidelines do not

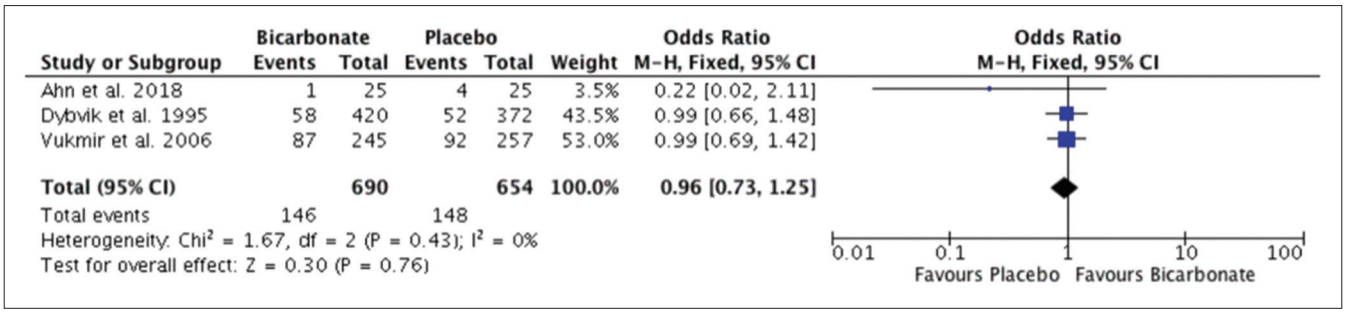

Figure 3: Forest plot comparing the odd ratios of survival to hospital admission between bicarbonate and placebo therapy in the whole cohort

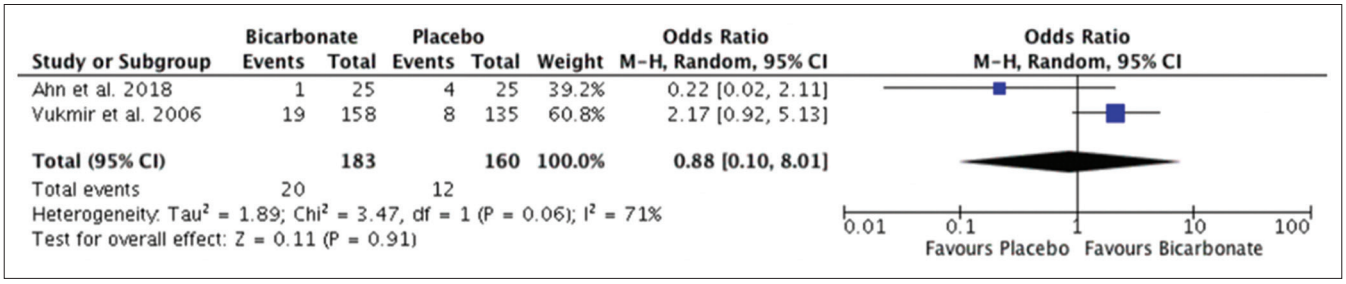

Figure 4: Forest plot comparing the odd ratios of survival to hospital admission between bicarbonate and placebo therapy in participants receiving prolonged cardiopulmonary resuscitation

recommend the routine administration of bicarbonates.[4] However, this following guideline still mentions the use of bicarbonates for correcting the metabolic acidosis, which is a reversible cause of CA. Because of the unclear indication of bicarbonate, some researchers tried to propose the availability of using bicarbonate or an appropriate indication for bicarbonate during resuscitation both in animal and human studies.[26-30]

Bicarbonate therapy for adults with CA receiving prolonged CPR has been controversial. Vukmir *et al*. found that bicarbonate therapy during prolonged CPR improved the rate of survival to hospital admission (OR = 2.17, P = 0.007).[9] However, after synthesizing these data with those obtained from another study,[21] such benefit could not be found.

Limitations

There were several limitations to this study. First, its sample size was small (n = 1344). Although there have been many retrospective and observational studies in this area, our meta-analysis focused only on the RCTs, which have a superior study design for minimizing the risk of bias especially in the therapeutic study. For this reason, only three trials could match with our inclusion criteria. In addition, two of three studies in the analysis have data collection periods that are very dated (Dybvik: 1987-1994; Vukmir: 1994-1998). The treatment protocols and emergency medical service systems in place at that time are quite contradictory to current guidelines. Second, the included trials did not report many outcomes recommended by the Utstein standard reporting guidelines. Some key outcomes of CPR were not available, including the rates of return of spontaneous circulation, survival to hospital discharge, and neurological outcome at discharge. Finally, the included trials applied different protocols of intervention (study participants, types of CA, and doses and times of administration). Therefore, no specific protocol of intervention can be recommended during bicarbonate administration. Despite these differences, we tried to separate and report as early and late administration which was already discussed.

Conclusion

For both acute and prolonged CPR, bicarbonate therapy might not show benefit to improve the rate of survival to hospital admission in adults with CA. Future trials should be carried out in larger sample sizes and include all outcomes recommended by the Utstein standard reporting guidelines.

Acknowledgment

We gratefully acknowledge Prof. Manit Srisurapanont for his comment on the drafted manuscript.

Author contributions statement

W.W. and K.S. conceived and contributed to the design and implementation of the research. W.W. processed the data, interpreted the results, drafted the manuscript, and designed the figures. K.S. performed the analysis. All authors discussed the results and commented on the manuscript.

Conflicts of interest

None declared.

Funding
None declared.

Ethical Consent
Not applicable

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