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Original Contribution

Sodium bicarbonate administration during ongoing resuscitation is associated with increased return of spontaneous circulation☆,☆☆,★

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ABSTRACT

Purpose: Sodium bicarbonate is frequently used for patients unresponsive to cardiopulmonary resuscitation (CPR). Its use may be associated with longer resuscitation duration as well as more severe metabolic acidosis. We applied a new analytical method based on a matched case-control study design to control for the potential confounders.
Basic procedures: Out-of-hospital cardiac arrest patients resuscitated in an emergency department for at least 20 minutes, unless there was any return of spontaneous circulation (ROSC) within the time frame, were analyzed. Patients without ROSC for 20 minutes of CPR were matched to those with ROSC based on initial bicarbonate level categorized using cutoff points of 10, 15, 20, 25, and 30 mEq/L, and their observation durations were trimmed to match their pairs. The association between sodium bicarbonate and ROSC was examined using conditional logistic regression analysis.
Main findings: Two matched groups, one with ROSC and the other without (both n = 258), were generated. Sodium bicarbonate administration and its total cumulative dose were significantly associated with an increased ROSC, with odds ratios for ROSC of 1.86 (95% confidence interval [CI], 1.09-3.16; $P = .022$) and 1.18 (per 20 mEq; 95% CI, 1.04-1.33; $P = .008$), respectively. The positive associations remained unchanged after multivariable adjustment, with odds ratios for ROSC of 2.49 (95% CI, 1.33-4.65; $P = .004$) and 1.27 (95% CI, 1.11-1.47; $P = .001$), respectively.
Principal Conclusion: Sodium bicarbonate administration during CPR in emergency department was associated with increased ROSC.

1. Introduction

The prognosis for an individual who suffers from an out-of-hospital cardiac arrest (OHCA) is very grave. Analysis of the Cardiac Arrest Registry to Enhance Survival revealed a survival rate to hospital admission of 26.3% and an overall survival rate to hospital discharge of 9.6% [1]. Because of the relative lack of effective treatments for OHCA, many treatments with only little or weak empirical support have been widely used as a desperate attempt to improve outcomes [2,3]. One such treatment is the administration of sodium bicarbonate during cardiopulmonary resuscitation (CPR). Although current guidelines strongly discourage the routine administration of sodium bicarbonate during CPR because of the lack of evidence in support of its efficacy [2,3], it has been commonly used during resuscitation of OHCA patients [4].

Because current American Heart Association guideline states that the bicarbonate therapy should be guided by the concentration of serum bicarbonate or calculated base deficit, patients treated with sodium bicarbonate may have more severe metabolic acidosis [2]. In addition, the medication may be used more frequently as a "last-ditch" effort in patients unresponsive to CPR [5]. Therefore, sodium bicarbonate might be associated with poorer outcomes regardless of its possible beneficial effect, and testing its effect on resuscitability using observational data would be difficult without an effective measure to control for confounders. In this study, we conducted a matched case-control study to evaluate the association between the use of sodium bicarbonate and the chance of achieving return of spontaneous circulation (ROSC). We hypothesized that the administration of sodium bicarbonate and its cumulative dose are positively associated with an increased chance of ROSC.

2. Materials and methods

This is a single-center observational study of OHCA patients resuscitated in the emergency department (ED) from January, 2008, to December, 2013. A prospective ED OHCA registry served as the primary data source. The institutional review board at the study site approved the analysis and waived the requirement of informed consent.

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2.1. Study setting

The study facility is an academic hospital located in a city with a population of 1 000 000 in South Korea with visits to the ED numbering more than 80 000 annually. Emergency medical services are provided by fire station-based emergency medical technicians hired by the government of South Korea [6]. The level of prehospital CPR is primarily restricted to basic life support, and therefore, administration of any medication (eg, epinephrine, atropine, amiodarone, and sodium bicarbonate) is not possible until ED arrival. Administration of sodium bicarbonate during CPR in the ED is at the discretion of the emergency physicians on duty. It is given by bolus injection of multiples of ampuls containing 20 mEq of sodium bicarbonate in a 20-cc solution. After ROSC, therapeutic hypothermia is recommended as a protocol if indicated.

2.2. Participants and data collection

The OHCA registry was analyzed by researchers to identify adult patients (≥18 years old) who received CPR upon ED arrival due to absence of pulse [7]. Patients with early termination within 20 minutes of advanced cardiac life support (ACLS) without any ROSC were excluded. Patient variables including age, sex, cardiac arrest location, presence of witness, bystander CPR, initial rhythm, and presumed cause of cardiac arrest were extracted from the registry. Results from initial blood gas analyses were retrieved from medical record review. Dose (in ampuls) and timing of administration of sodium bicarbonate were collected from nurse-documented CPR log sheets. The time points of either the first ROSC or of termination without any ROSC were also retrieved from the same source.

2.3. Statistical analysis

This is a matched case-control study in which the outcome variable is achievement of ROSC and exposure variables of interest include the administration of sodium bicarbonate and its cumulative dose in the patient population where CPR was continued for at least 20 minutes or until ROSC occurred.

We selected 2 major potential confounders at the beginning of the study and controlled them using the following methods (Fig. 1). The first major confounder was the severity of metabolic acidosis. We controlled for this by matching patients with ROSC to those without ROSC based on their initial blood bicarbonate levels categorized by cutoff points of 10, 15, 20, 25, and 30 mEq/L. The process used a one-to-one ratio without replacement. The choice of initial bicarbonate level as a major confounder arose from our assumption that it would be the most important factor in determining the amount of sodium bicarbonate administered because of the guideline statement that sodium bicarbonate therapy should be guided by the bicarbonate concentration or calculated base deficit [2]. The second major confounder was observation (CPR) duration. If the use of sodium bicarbonate tends to be a "last-ditch" effort for patients who are unresponsive to prolonged resuscitation efforts, then the duration of CPR should act as a significant confounder. We controlled for the difference in CPR duration within the study population by limiting the observation duration in the unresponsive patients to that of their paired patients with ROSC.

After these processes, we examined the administration of any dose of sodium bicarbonate as well as its total cumulative dose during the observation time frame. The relationships of these to ROSC were tested using both univariable and multivariable conditional logistic regression analysis. This process was to control other possible confounders that were not considered in the initial matching process. Independent variables with a P value less than .1 in the univariable analysis were included in the multivariable analysis for model parsimony. We also constructed full models including all available variables to see if there is any significant change in parameter estimates. P values less than .05 were considered significant. All analyses were performed using the R package version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

A total of 771 adult OHCA patients were transferred to the ED. Of these, 738 patients who were without prehospital ROSC received ACLS in the study ED. After the exclusion of patients whose resuscitation efforts were terminated without any ROSC within 20 minutes of ED ACLS (n = 76; 10.3%) and patients without an initial blood gas analysis before ROSC (n = 63; 8.5%), a total of 599 (81.2%) patients were eligible for analysis. Baseline characteristics of the study patients are summarized in Table 1. There were significant group differences between patients with ROSC within 20 minutes (n = 331; 55.3%) and patients without ROSC (n = 268; 44.7%). Specifically, patients with ROSC were more likely to have witnessed cardiac arrest (77.3% vs 56.7%, $P < .001$) and have a presumed noncardiac etiology (63.7% vs 50.7%, $P = .002$), as well as have higher initial pH (7.00 vs 6.96 $P = .010$), higher Pao_2 (55.2 mm Hg vs 32.7 mm Hg, $P < .001$), lower initial $Paco_2$ (66.5 mm Hg vs 72.0 mm Hg, $P < .001$), and shorter median ED ACLS duration (until ROSC or termination; 9 minutes vs 30 minutes, $P < .001$). Administration of any dose of sodium bicarbonate and its cumulative dose during ED ACLS (until first ROSC or termination) were also significantly different between patient groups, showing their association with a decreased chance of ROSC (Table 1).

Patients in each group were matched based on the initial bicarbonate level, and time frame of observation for each matched pair was made identical by trimming the excess duration of CPR in unresponsive patients (Table 2). In univariable conditional logistic regression analysis, all patient and laboratory variables showed a similar pattern of association as observed in the unmatched population; however, the direction of association of both the administration of sodium bicarbonate and its cumulative dose were reversed, with their odds ratios (OR) for ROSC of 1.86 and 1.18 and 95% confidence intervals (CIs) of 1.09 to 3.16 ($P = .022$) and 1.04 to 1.33 ($P = .008$), respectively. Fig. 2 illustrates the differences in the use of sodium bicarbonate between patients with and without ROSC during observation time frames categorized into <0 and ≤5, >5 and ≤10, >10 and ≤15, and >15 and ≤20 minutes.

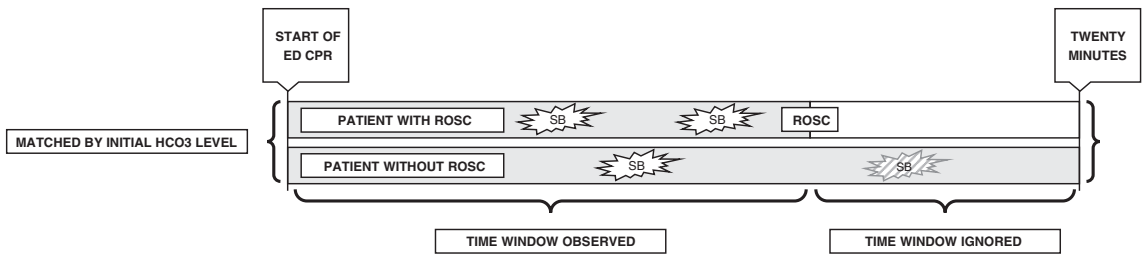

Fig. 1. An illustration showing how potential confounders were controlled. A, We controlled for different severities of metabolic acidosis by matching patients with ROSC to those without ROSC based on their initial bicarbonate levels. B, Different CPR durations were controlled by limiting the observation duration in unresponsive patients to that of their paired patients with ROSC. Abbreviation: SB, sodium bicarbonate.