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Clinical paper

Testosterone related good neurologic outcome on the patients with return of spontaneous circulation after cardiac arrest: A prospective cohort study☆

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ABSTRACT

Aim: To evaluate the gonadal hormones in patients with return of spontaneous circulation (ROSC) after cardiac arrest following prospectively good (cerebral-performance category [CPC] 1-2) and poor (CPC 3-5) neurologic outcomes.
Methods: The patients in an emergency center who had been admitted to the center's intensive care unit (ICU) after successful resuscitation following out-of-hospital cardiac arrest were prospectively identified and evaluated within the period from April 2008 to March 2011. The gonadal hormones, including progesterone, total estrogen, and testosterone, were measured and analyzed following the good and poor neurologic outcomes.
Results: A total of 142 patients were analyzed in this study. Thirty-nine (27.5%) patients had good neurologic outcomes. The gonadal hormones (progesterone, total estrogen, and testosterone) had good vs. poor neurologic outcomes of 1.039 ± 0.694 vs. 1.000 ± 0.892 ng/ml, 107.956 ± 13.163 vs. 117.060 ± 11.344 pg/ml, and 307.380 ± 33.844 vs. 189.020 ± 17.406 ng/dl, respectively. In the multiple logistic-regression analysis, the initial shockable rhythm (5.671 odds ratio [OR], 2.307-13.942 95% confidence interval [CI]), time from arrest to ROSC (0.957 OR, 0.933-0.982 95% CI), and more than 300 ng/dl of testosterone level (3.279 OR, 1.265-8.190 95% CI) were found to be related to good neurologic outcome, respectively.
Conclusion: Higher testosterone levels are related to good neurologic outcome at six months after admission in patients with spontaneous circulation after cardiac arrest. The testosterone levels may be useful prognostic tools for the postcardiac-arrest syndrome and could be used for the latter's neuroprotective treatment, but additional randomized controlled studies are needed.

1. Introduction

Out-of-hospital cardiac arrest is fatal, and the fact that its cases are increasing has become a serious concern. There were approximately 166-200 out-of-hospital cardiac-arrest cases in the U.S. in 2008,[1] and the standardized incidence rates in South Korea in 2006 and 2007 were 20.9 and 22.2 per 100,000, respectively.[2] The survival discharge rate was extremely low (3.5%) for the resuscitation-attempted group, and only 1.1% of all the patients had a favorable neurologic outcome (cerebral performance category [CPC] 1-2).[2] The importance of postcardiac-arrest care in lowering the mortality and the subsequent neurologic outcome has significantly increased.[3] The 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation emphasized the integrated postcardiac-arrest care with the last chain of survival.[4] Two randomized clinical trials and a meta-analysis showed improved outcomes in adults who remained comatose after initial resuscitation from out-of-hospital ventricular-fibrillation (VF) cardiac arrest, and who were cooled within minutes to hours after return of spontaneous circulation (ROSC).[5,6] Except for therapeutic

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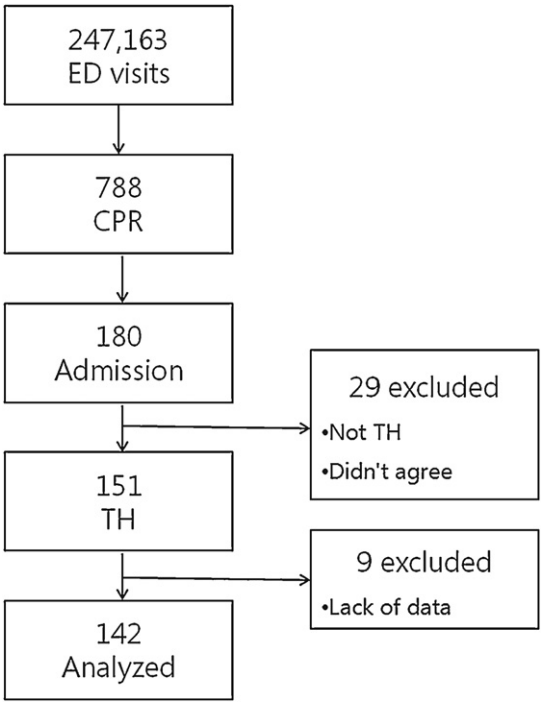

Fig. 1. This is the enrolled diagram during study period (ED: emergency department; CPR: cardiopulmonary resuscitation; TH: therapeutic hypothermia).

hypothermia, however, the clinical trials failed to prove improved neurological outcomes with neuroprotective drugs after cardiac arrest.[7]

The most well-known neuroprotective hormones are the gonadal hormones, including progesterone, estrogen, and testosterone, in various animal ischemia models.[8–11] The primary objective is this study was to evaluate whether higher testosterone level is related to good neurologic outcome in post-cardiac arrest syndrome with therapeutic hypothermia in patients with ROSC after out-of-hospital cardiac arrest, and secondary objective was to evaluate whether other gonadal hormones including progesterone and estrogen level are related to good neurologic outcome in post-cardiac arrest syndrome with therapeutic hypothermia in patients with ROSC after out-of-hospital cardiac arrest.

2. Methods

2.1. Study population

The study institution was a 1600-bed university hospital with an annual emergency intensive care unit (EICU) census of 1000. This was a prospective study of patients with ROSC (>24 h) after out-of-hospital cardiac arrest who were older than 16 years of age and who had been admitted to the EICU for over a 36-month period, between August 2008 and July 2011 (Fig. 1). Patients receiving gonadal-hormonal-replacement therapy, who died within 24 h from their hospital admission, who received trauma, and who were pregnant were excluded from the study. This study was approved by the institutional review board of these authors' center (GIRBA 2452), and informed consent for blood sampling and for participation in the study was obtained from the patients' next of kin, following the protocol used in these authors' department. In these authors' emergency center, the standardized postcardiac-arrest care protocols have been used since 2007 and are updated annually.

2.2. Clinical evaluation and outcomes

The basal characteristics of the patients were obtained from the laboratory results in the medical records. The 90-day mortality and the neurologic outcomes (CPC) at six months after discharge were evaluated. CPC 1 and 2 were categorized as good neurologic outcomes.

2.3. Gonadal-hormone concentrations

The blood of each patient was sampled at about 8:00 a.m. on the day following admission to the EICU (between 12 and 24 h after ROSC). The sampled blood was centrifuged, separated from the plasma, and kept in a −70 °C deep freezer. The gonadal-hormone concentrations, including those of progesterone, total estrogen, and testosterone, were measured via chemiluminescence immunoassay (CLIA).

In the results of pilot study, the cut-off value of testosterone is roughly 300 ng/dl. After receiving informed consent, gonadal hormones were measured, and the results were managed by tester.

2.4. Statistical analysis

Sample size was calculated that at least 135 patients should be enrolled in this study (if $\alpha = 0.05$, $\beta = 0.15$, power = 0.85). If drop-out rate is expected to be 0.2, at least 169 patients are needed in this study. The data were analyzed using the SPSS software (version 16.0; SPSS, Inc., Chicago, IL, USA). The t-test and chi-square test were used, and single- and multiple-logistic-regression-model analyses were performed to estimate the odds ratios (ORs) of the neurologic outcomes, along with 95% confidence intervals (CIs). Cox regression analysis was performed to evaluate the 90-day mortality with 95% CI. Statistical significance was defined as a p value of <0.05.

3. Results

During the study period, total 247,163 patients visited our emergency department and 788 patients were received cardiopulmonary resuscitation. Among these, 180 patients were admitted emergency department intensive care units and received post-cardiac arrest care. Twenty-nine patients were excluded due to not being received therapeutic hypothermia, and 9 patients were excluded by lack of data. So, a total of 142 patients were analyzed in this study (Fig. 1). The basal characteristics of the patients are shown in Table 1. There were 98 (69.0%) males, and their mean age was 53.33 (±15.242) years old. Thirty-nine (27.5%) patients had good neurologic outcomes. The factors that were found to be related to good CPC were male gender, height, body weight, initial shockable rhythm, cardiac cause of cardiac arrest, time from arrest to start of basic life support (AR_BLS), time from arrest to start of advanced cardiac life support (AR_ACLS), time from arrest to ROSC (AR_RO), acute physiology and chronic health evaluation (APACHE) II score, and testosterone concentrations in the univariate analysis (Table 2). The multiple logistic regressions by mortality and CPC are shown in Tables 3 and 4. The factor that was found to be related to 90-day mortality in the Cox regression analysis was initial shockable rhythm (Table 3). Statistically, the gonadal-hormone concentrations were not significantly related to mortality. In the multiple logistic-regression analysis, the initial shockable rhythm, time from arrest to ROSC, and more than 300 ng/dl of testosterone level were found to be related to good neurologic outcome, respectively (Table 4). Other gonadal-hormone concentrations, including progesterone and total estrogen, were not related to good neurologic outcomes. The cut-off values of the testosterones were