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Original Contribution

Effect of valproic acid combined with therapeutic hypothermia on neurologic outcome in asphyxial cardiac arrest model of rats☆

Jae Hyuk Lee, MD, PhD [a], Kyuseok Kim, MD, PhD [a,*], You Hwan Jo, MD, PhD [a], Min Ji Lee, BS [a], Ji Eun Hwang, MD [a], Min A. Kim, MD, PhD [b]

[a] Department of Emergency Medicine, Seoul National University Bundang Hospital, Gyeonggi-do, Republic of Korea
[b] Department of Pathology, Seoul National University, Seoul, Republic of Korea

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ABSTRACT

Backgrounds: Valproic acid (VPA) has been reported to have survival and neuroprotective effects in a cardiac arrest rat model. This study was designed to investigate the effect of VPA combined with therapeutic hypothermia (HT) in an asphyxial cardiac arrest rat model.

Methods: Rats were subjected to 6 minutes of asphyxial cardiac arrest. Cardiopulmonary resuscitation was performed and then the randomly allocated to 1 of 4 groups (normal saline [NS]/normothermia [NT], VPA/NT, NS/HT, and VPA/HT). Hypothermia (32.5°C ± 0.5°C, 4 hours of HT and 2 hours of rewarming) or NT (37°C ± 0.5°C for 6 hours) was applied, and VPA (300 mg/kg) or NS was administered immediately after the return of spontaneous circulation. Neurologic deficit score was measured, and a tape removal test was performed for 3 days. Histologic injury of hippocampus was evaluated.

Results: Valproic acid significantly improved neurologic deficit score at 48 and 72 hours in the NT-treated rats and at 72 hours in the HT-treated rats (all $P < .05$). Although the latency and success rate were not significantly different between the VPA/NT and NS/NT groups, the VPA/HT group showed significantly lower latency and higher success rates compared to the NS/HT group ($P < .05$). The histologic injury score in the hippocampal CA1 sector was significantly lower in the VPA/NT group than the NS/NT group ($P < .05$) and showed a tendency to be decreased in the VPA/HT group compared with the NS/HT group ($P = .06$).

Conclusion: In an asphyxial cardiac arrest rat model, administration of VPA improved neurologic outcomes and added a neuroprotective effect to HT.

1. Introduction

Cerebral injury after cardiac arrest remains as a significant health care problem [1]. Although an understanding of pathophysiology and improvement of resuscitation techniques have led to significantly improved outcomes in cases of out-of-hospital cardiac arrest [2], therapeutic intervention for cerebral injury after cardiac arrest remains suboptimal. Therefore, a more sophisticated therapeutic intervention is needed to improve outcomes in patients with cardiac arrest.

It has been reported that valproic acid (VPA) as a histone deacetylase inhibitor has neuroprotective effects in animal models of ischemic cerebral injury [3-5]. In addition, therapeutic hypothermia (HT) is a clinically proven therapeutic measure to decrease cerebral injury and is recommended in practice guidelines [6-9]. Recently, it has been reported that VPA and therapeutic HT showed a synergistic neuroprotective effect on hypoxic hippocampal cell (HT-22 cells) injury [10]. However, the combined effect of these neuroprotective treatments in cases of cardiac arrest–induced brain injury has not been reported.

This study was designed to evaluate the neuroprotective effect of VPA combined with therapeutic HT in an asphyxial cardiac arrest rat model.

2. Materials and methods

The institutional animal care and use committee approved the study.

2.1. Animal preparation

Male Sprague-Dawley rats weighing 300 to 350 g were used in the experiments. Before the experiments, the rats were housed in a controlled environment with free access to water and food. The method of animal preparation has been described previously [5]. Briefly, rats were anesthetized using intramuscular injection of zoletil (30 mg/kg) and xylazine (15 mg/kg) and intubated with a 16-gauge catheter (BD Insyte Autoguard, Franklin Lakes, NJ). Rats were mechanically ventilated with a rodent ventilator (tidal volume, 2 mL; respiratory rate, 55 per minute; fraction of inspired oxygen, 0.21; Harvard rodent ventilator model 645, Harvard apparatus, Holliston, MA), and minute ventilation

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* Corresponding author at: Department of Emergency Medicine, Seoul National University Bundang Hospital, 300 Gumi-dong, Bundang-gu, Seongnam-si, Gyeonggi-do, 463-707, Republic of Korea. Tel.: +82 31 787 7579; fax: +82 31 787 4055.
E-mail address: dremkks@snubh.org (K. Kim).

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was adjusted to ensure $Paco_2$ between 35 and 40 mm Hg according to the result of blood gas analysis. Intravascular catheters (24 gauge; BD Insyte Autoguard) were inserted in the left femoral artery for blood pressure monitoring and blood sampling (for blood gas analysis) and in the tail vein for drug administration.

2.2. Cardiac arrest and cardiopulmonary resuscitation

Induction of asphyxial cardiac arrest and cardiopulmonary resuscitation (CPR) has been described previously [5]. Briefly, vecuronium was administered, and the mechanical ventilator was disconnected to induce respiratory arrest. *Circulatory arrest* was defined as the onset of mean arterial pressure decline to 20 mm Hg and was maintained for 6 minutes.

After 6 minutes of circulatory arrest, CPR was performed. Resuscitation consisted of resuming mechanical ventilation (tidal volume, 2 mL; fraction of inspired oxygen, 1.0; respiratory rate, 55 per minute), administering intravenous epinephrine (0.01 mg/kg) and bicarbonate (1.0 mEq/kg), and performing continuous external chest compressions at a rate of 200 compressions per minute using a mechanical thumper (custom-made device, compressed air-driven, rate was set at 200 cycles/min) until spontaneous pulse was observed in arterial tracing and mean arterial pressure greater than 50 mm Hg was reached. After the return of spontaneous circulation (ROSC), rats were observed and maintained using mechanical ventilation.

2.3. Inclusion and exclusion criteria

The objective of this study is to evaluate the neuroprotective effect of VPA administered just after ROSC and combined with HT in asphyxia cardiac arrest. Therefore, rats that were successfully resuscitated from cardiac arrest and weaned from mechanical ventilation after 6 hours of postresuscitation care were included; rats were excluded if cardiac arrest induction time was longer than 3 minutes to control hypoxia duration and if mechanical ventilation was not weaned after 6 hours of postresuscitation care. In our previous reports, 6 minutes of cardiac arrest resulted in successful weaning of mechanical ventilation [5].

2.4. Study group allocation and postresuscitation care

After ROSC, rats were randomly allocated to 1 of 4 groups (normal saline [NS] + normothermia [NT] group; VPA + NT [VPA/NT] group; NS + HT [NS/HT] group; VPA + HT [VPA/HT] group) (Fig. 1). Just after the ROSC, VPA (300 mg/kg) or vehicle (same amount of NS) was administered via tail vein and HT (target temperature, 33°C ± 0.5°C) was induced using ice slurry and a fan and maintained for 4 hours. Thereafter, rewarming was performed actively for 2 hours using a heating fan. Body temperature of rats in the NT group was maintained at 36.5°C to 37.0°C during 6 hours of postresuscitation care. If adequate spontaneous respiration could be recovered after 6 hours of postresuscitation care, the mechanical ventilator was disconnected.

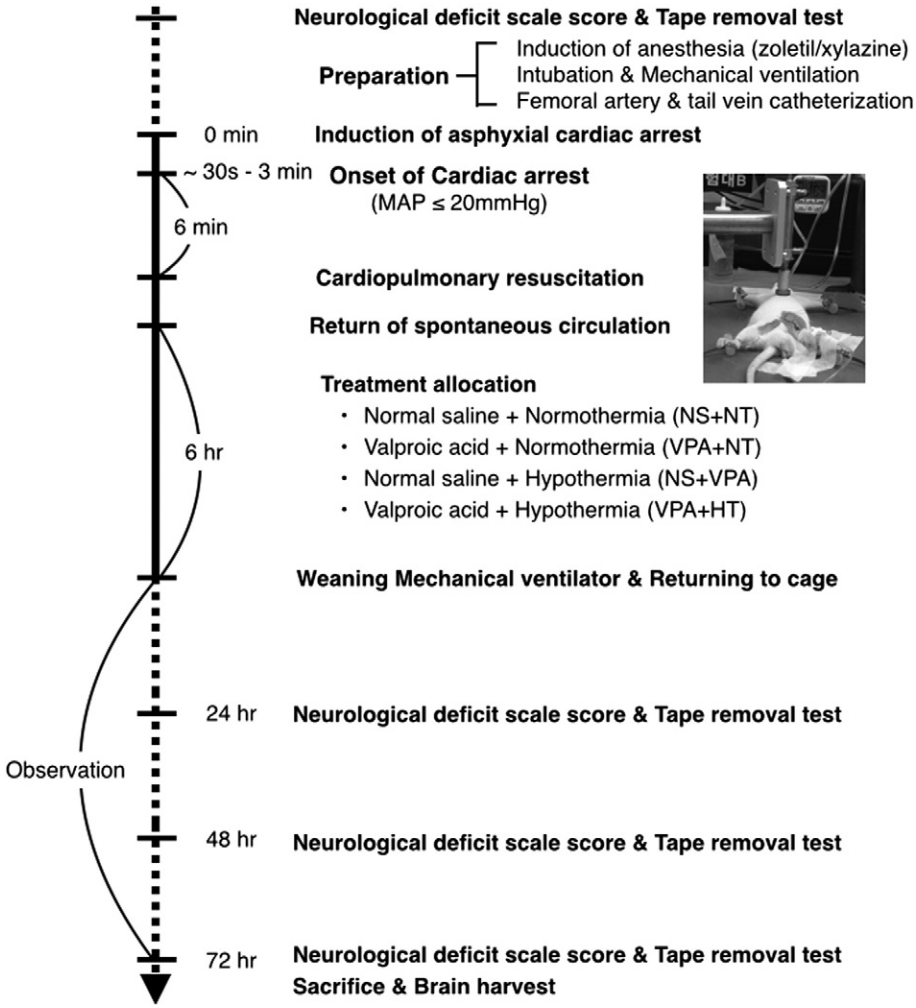

Fig. 1. Timeline of experiment.