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Clinical paper

Differential effect of mild therapeutic hypothermia depending on the findings of hypoxic encephalopathy on early CT images in patients with post-cardiac arrest syndrome☆

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ABSTRACT

Introduction: The aim of this study was to evaluate the differential effects of mild therapeutic hypothermia (MTH) in post-cardiac arrest syndrome (PCAS) patients depending on the presence/absence of hypoxic encephalopathy (HE) in the early brain CT images obtained before the initiation of MTH.
Methods: We conducted a retrospective review of the data of a total of 129 patients with PCAS who were treated by MTH (34 °C) or normothermia treatment (NT) (35 °C or 36 °C), and had undergone brain CT examination prior to the initiation of these treatments. We divided the subjects into 4 groups, namely, the HE(−)/MTH, HE(−)/NT, HE(+)/MTH, and HE(+)/NT groups, for evaluating the interaction effect between the two variables. Then, we compared the neurological outcomes between the HE(−)/MTH and HE(−)/NT groups by multivariate logistic analysis. Good outcome was defined as a Cerebral Performance Category score of ≤2 at 30 days.
Results: The percentages of subjects with a good outcome in the HE(−)/MTH and HE(−)/NT group were 68.9% (42/61) and 36.1% (13/36), respectively (p = .003), while those in the HE(+)/MTH and HE(+)/NT groups were lower, at 7.4% (2/27) and 20.0% (1/5), respectively (p = .410), suggesting a statistically significant interaction effect between the two variables ($p_{interaction}$ = 0.002). In the HE(−) group, MTH was associated with a higher odds ratio of a good outcome as compared to NT (OR 6.80, 95% CI 1.19–38.96, p = .031).
Conclusions: The effect of MTH in patients with PCAS differed depending on the presence/absence of evidence of HE on the early CT images.

Introduction

Even since it was demonstrated in two large randomized clinical trials that mild therapeutic hypothermia (MTH) improved the outcome of patients with post-cardiac arrest syndrome (PCAS) [1,2], a number of hospitals have begun to use MTH for the treatment of PCAS. However, a recent trial showed no beneficial effect of MTH as compared to normothermia treatment (NT) [3]. Therefore, the effectiveness of MTH as compared to NT in patients with PCAS remains uncertain [4].

One of the possible reasons why the aforementioned study failed to show a beneficial of MTH despite the demonstration in numerous animal studies of improvement of the neurological outcomes of PCAS by MTH treatment [5–7] is that the subject population in that study included PCAS patients of all grades, including the highest grade, of severity [3]. Logically, the effect size of MTH would be expected to differ according to the severity of PCAS, and the neurological outcomes of patients who already have major irreversible damage of the brain prior to the treatment may fail to improve with MTH. If the analysis were limited to PCAS patients in whom the condition is not too severe and is likely to respond for the treatment, MTH could possibly be determined to be more effective as compared to NT.

A few groups investigated the differential effect of MTH depending on the severity of PCAS as assessed by the time to return of spontaneous circulation, but the results remain under debate [8,9]. While Kaneko T. et al. showed that a lower targeted temperature during MTH was associated with good neurological outcomes if the downtime was ≤30 min [8], Kjaergaard J et al. showed no impact of the time to return of their spontaneous circulation on the effect of MTH as compared to

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that of NT [9]. However, the time to return of spontaneous circulation may not be an appropriate marker of the severity of PCAS in actual clinical practice, as the severity can also be influenced by many pre-hospital factors, including the cardiac arrest time. Therefore, a more suitable scale for estimating the severity of PCAS is needed.

Under this circumstance, early brain CT may be one of the most useful tools for estimating the severity of PCAS. In actual clinical practice, we usually perform early brain CT prior to the start of treatment, to estimate the severity in PCAS patients [10] and to rule out any cerebral cause for the cardiac arrest [11]. Evidence of hypoxic encephalopathy (HE) on the early CT images is reported as an important and reliable sign of a poor prognosis [12–14]. Several studies have shown that the neurological outcomes in patients with early-CT evidence of HE remain poor, even if they have received MTH [15]. This result may imply that early brain CT in PCAS patients is useful for detecting the most severe cases, or conversely, for identifying patients without HE who are more likely to be responsive to MTH. The aim of the present study was to investigate whether MTH exerts differential effects in PCAS patients depending on the presence or absence of evidence of HE on the early brain CT images, and to evaluate the effect of MTH as compared to NT in PCAS patients without evidence of HE in the early CT images.

Methods

Study design

We conducted this double-center, retrospective observational study in adult PCAS patients admitted to the intensive care unit (ICU) for the treatment of therapeutic hypothermia between 2011 and 2017. All the eligible patients had undergone brain CT prior to the initiation of treatment. Patients for whom the radiologists' interpretation of the CT images was unavailable were excluded from the study. Patients who required extracorporeal membrane oxygenation because of hemodynamic instability were also excluded. This study was conducted in the remaining patients with the approval of the research ethics boards of Nagoya University Hospital and Red Cross Maebashi Hospital.

Participating hospitals

This study was performed at the ICUs of Nagoya University Hospital and Japan Red Cross Maebashi Hospital, both tertiary emergency medical centers (Japanese centers for emergency patients with serious or life-threatening conditions). The hospitals, with 1035 and 592 beds, including 26 and 12 ICU beds, respectively, are located in cities. They treat about 12,000 and 20,000 emergency patients each year, respectively.

Dataset

Data, including the clinical histories, cardiac rhythms, physical examination findings, results of blood examinations, and clinical courses after admission, were collected retrospectively from the electronic medical charts. We also reviewed the radiologists' reports of the brain CT images of the subjects in order to collect data about the presence/absence of HE on the early brain CT images. When phrases such as "signs of loss of gray-white matter differentiation" or "brain swelling was seen" were found in the report, we judged that the early CT showed evidence of HE. The CT was performed using an Aquilion64 (TOSHIBA) in all the cases at the Nagoya University Hospital, and using SOMATOM Definition Flash (SIEMENS) in all the cases at the Japan Red Cross Maebashi Hospital, prior to the initiation of treatment (MTH or NT). The longest interval between the cardiac arrest event and CT in the subjects was 6 h.

Protocol for therapeutic hypothermia

Eligible patients received MTH according to the protocol at the respective hospitals. MTH was considered for cardiac arrest patients who were in a coma (GCS ≤ 8) after the return of spontaneous circulation, without remarkable hemodynamic instability or a "Do Not Attempt to Resuscitation" directive. The following patients were excluded: patients with traumatic cardiac arrest, pediatric age-group patients (age < 18 years), and patients who were not living independently prior to the cardiac arrest. The target core temperature was set at 34 °C, 35 °C or 36 °C, achieved by infusion of cold fluids and a surface cooling device with computerized automatic temperature control (Arctic Sun 2000 TTM; Bard Medical Louisville, CO). We defined targeted temperature management at 34 °C as MTH and that at 35 °C or 36 °C as NT. After maintaining the target temperature for 24 h, rewarming to 36 °C was performed at the rate of 1 °C/24 h. Propofol, dexmedetomidine, midazolam, fentanyl and rocuronium were used for sedation, analgesia and muscle relaxation, respectively, according to the individual attending clinicians' preferences. In therapeutic hypothermia treatment, the ventilator settings, fluid infusion rates, and doses of vasopressor, sedative, and analgesic agents are adjusted so that the mean arterial pressure is maintained at ≥80 mm Hg, the pCO2 is maintained in the range of 35–45 mm Hg, and the urine output is maintained at ≥0.5 mL/kg/h, in order to maintain cerebral perfusion. No changes to the protocol were made during the study period.

Neurological outcome

We used the Cerebral Performance Categories (CPC) at 30 days to estimate the neurological outcome, as follows: CPC 1, full recovery; CPC 2, moderate disability; CPC 3, severe disability; CPC 4, coma or vegetative state; CPC 5, died [16]. We calculated the CPC score at 30 days by reviewing the electronic charts. For the purpose of our study, CPC 1–2 was considered as representing a good outcome, while CPC 3–5 was considered as representing a poor outcome (3–5) [16].

Statistical analysis

Fisher's exact test and Mann-Whitney's *U* test were used to compare the categorical data and ordinal variables, respectively. To confirm the interaction effect between the targeted core temperature and presence/absence of evidence of HE on the early CT images, we performed multivariate logistic analysis with adjustments for 6 prespecified covariates that were considered as potentially exerting significant influence on the neurological outcome in cases of PCAS, namely, (1) age > 60/≤60 years, (2) age > 80/≤80 years, (3) initial rhythm, (4) presence/absence of bystander assistance, (5) presence/absence of witnesses and downtime, and (6) type of hospital admitted to. Multivariate logistic regression analysis in the HE (−) group was performed to estimate the association between the targeted core temperature and neurological outcome, with adjustments performed for the same 5 prespecified covariates. There were no missing values and we did not perform any imputations. All the reported P values were two-sided, and $P < 0.05$ was regarded as denoting a statistically significant difference. All analyses were conducted using the SAS software, version 9.4 (SAS Institute, Cary, NC).

Results

A total of 156 PCAS patients were admitted to the participating ICUs for the initiation of MTH or NT during the study period. Of these, 27 were excluded because early brain CT was not performed prior to the initiation of treatment (n = 8), extracorporeal membrane oxygenation was needed for maintenance of hemodynamic stability (n = 15), or records of interpretation of the CT images were not available (n = 4). The remaining 129 patients were included in this study (Fig. 1).