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Comparison of whole-body cooling and selective head cooling on changes in urinary 8-hydroxy-2-deoxyguanosine levels in patients with global brain ischemia undergoing mild hypothermia therapy

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A Study Design
B Data Collection
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Summary

Background: We evaluated changes in the levels of urinary 8-hydroxy-2-deoxyguanosine (8-OHdG) in patients undergoing mild hypothermia therapy and compared 8-OHdG expressions in those receiving whole-body cooling or selective head cooling.

Material/Methods: The subjects were 15 patients undergoing mild hypothermia therapy following resuscitation after cardiac arrest in our intensive care unit. We divided the patients into 2 groups receiving either whole-body cooling or selective head cooling, according to their circulatory stability. We examined urinary 8-OHdG level for 1 week and neurological outcomes 28 days after admission.

Results: We observed significant decreases in urinary 8-OHdG levels on days 6 and 7 compared with that on day 1 in the whole-body cooling group. Furthermore, we noted significantly lower urinary 8-OHdG levels after days 5, 6 and 7 in the whole-body cooling group than in the selective head-cooling group. Neurological outcomes were similar in both groups.

Conclusions: Mild hypothermia therapy with whole-body cooling had a greater effect on the suppression of free radical production than selective head cooling. However, selective head cooling might be an appropriate indication for patients with circulatory instability after resuscitation, because it provides neuroprotection similar to that of whole-body cooling.

key words: **mild hypothermia therapy • free radicals • selective head cooling**

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Background

Mild therapeutic brain hypothermia has been reported to improve neurological outcomes after cardiac arrest (CA), and it has recently been widely used as a treatment component for neuroprotection after resuscitation [1–4].

Brain damage following cerebral hypoxia-ischemia and reperfusion is mediated by several mechanisms. In particular, oxygen-free radicals play important roles in global brain ischemia after CA. The aim of brain hypothermia therapy is to suppress the generation of free radicals and improve the neurological outcome [5].

Brain hypothermia therapy with whole-body cooling may induce various adverse effects such as circulatory instability, infection and disseminated intravascular coagulation. Brain hypothermia therapy with selective head cooling has been reported to be effective after CA in an animal model [6]. Furthermore, rapid and selective brain hypothermia has been achieved using a cooling helmet in patients after a stroke or head injury [7].

8-Hydroxy-2-deoxyguanosine (8-OHdG) is a biomarker of DNA damage induced by oxidative stress [8]. The aims of the present study were to examine the changes in the levels of urinary 8-OHdG during brain hypothermia therapy and to compare 8-OHdG expressions between whole-body cooling and selective head cooling.

Material and Methods

The subjects were 15 patients undergoing mild brain hypothermia therapy following resuscitation in our intensive care unit (ICU) within the period from 2006 to 2007. The inclusion criteria were as follows: spontaneous circulation had been restored within 20 minutes after cardiac collapse [associated with ventricular fibrillation (VF) ventricular tachycardia (VT) or peak endocardial acceleration (PEA)] occurring either in or out of hospital; within the age range of 18 to 75 years; and Glasgow Coma Scale (GCS) scores between 4 and 8, inclusively. All subjects survived for more than 14 days after ICU admission. Patients with severe diabetes mellitus, liver dysfunction or renal insufficiency, or who had received steroid therapy were excluded. This study was approved by the Ethics Committee of Tokyo Medical University. Written informed consent of the patients' families was obtained regarding the protocol of this study.

We divided the patients into 2 groups: a whole-body cooling group which had circulatory stability [systolic blood pressure (SBP) >90 mm Hg and required no catecholamines], and a selective head-cooling group which had circulatory instability (SBP <90 mm Hg, or required catecholamines or had shown repeated VT or VF episodes). There were 7 patients treated with whole-body cooling (5 men and 2 women) and 8 treated with selective head cooling (6 men and 2 women). We started the induction of mild brain hypothermia within 3 hours of their ICU admission.

Whole-body cooling procedures

The induction of mild hypothermia at 34°C (based on tympanic membrane temperature) was started using a water cooling blanket, the rapid infusion of cooled saline, and gastric lavage with cooled saline. Patients were sedated and mechanically ventilated with fentanyl (0.025–0.05 mg/h) and midazolam (3–7 mg/h). Vecuronium bromide (3–5 mg/h) was given as a muscle relaxant. We discontinued sedation and started the rewarming phase by increasing the temperature by increments of 0.5°C to 1.0°C/day after maintaining mild hypothermia for 24 to 48 hours.

Selective head cooling procedures

The induction of mild hypothermia at 34°C (based on tympanic membrane temperature) was started using a cooling helmet (Medicool MC 2100, MAC8, Medical Systems, Tokyo, Japan). This cooling helmet has a thermostat control system combined with a probe for monitoring tympanic membrane temperature. Initially, we maintained a temperature of 5°C, using cooling water inside the helmet for induction. Patients were sedated with midazolam (3–5 mg/h) only if shivering or convulsions occurred. We started the rewarming phase by increasing the temperature by increments of 0.5°C to 1.0°C/day after maintaining mild hypothermia for 24 to 48 hours. We adjusted and maintained the temperature at 10°C using the helmet and removed it when the temperature of the tympanic membrane reached the optimal rewarming temperature. The International Liaison Committee on Resuscitation (ILCOR) guidelines recommend 12 to 24 hours of hypothermia after VF [9]. However, in our institution, we have little experience in starting early rewarming in hypothermia therapy, and therefore, we decided to start rewarming 24 to 48 hours after the start of hypothermia. Recent investigations have shown that slow rewarming is beneficial for neuroprotection [10].

We did not observe any instances of shivering in the whole-body cooling group with sedative medicine. We observed shivering in only a few cases in the selective head-cooling group. In those cases, we managed the shivering with an infusion of low-dose midazolam (1–2 mg/hour).

Management of blood sugar, electrolyte and fluid levels

We measured serum electrolyte and blood sugar levels every 4 hours during hypothermia therapy. We corrected electrolyte levels by fluid management and blood sugar imbalances to within 120–180 mg/dl by sliding insulin (Humarin, Shionogi, Tokyo, Japan) therapy. We determined the volume of fluid required following blood pressure and central venous pressure evaluation.

We measured the durations of the induction and rewarming periods, and the neurological outcomes 28 days after ICU admission. We collected 10 ml of urine every morning and the urine samples were frozen at –40°C. The levels of urinary 8-OHdG were measured using a high-performance liquid chromatography system equipped with a CoulAray detector (M.C. Medical, Tokyo, Japan) for 1 week. The levels of urinary 8-OHdG were adjusted for the levels of serum creatinine.

The data are expressed as means ± standard deviation Statistical analysis was performed using the Mann-Whitney U-test and Friedman's χ^2 test. A p-value of less than 0.05 was considered to represent a statistically significant difference.

Table 1. Patient characteristics.

Group	Age	Gender	GCS	APACHE II	Diahnosis
Whole-body cooling	40.3±6.7*	Men: 5 Women: 2	5.6±1.6	17.9±3.7	VT: 1 VT/VF: 2 VF: 3 PEA: 1
Selective head cooling	52.8±4.7	Men: 6 Women: 2	5.8±2.1	15.5±2.6	VT: 1 VT/VF: 1 VF: 4 PEA: 2

Data are expressed as means ± standard deviation (S.D.). * A significant difference was observed between the groups with the Mann-Whitney U-test ($P<0.05$). GCS – Glasgow Coma Scale; APACHE II – Acute Physiological and Chronic Health Evaluation.

Table 2. Induction and rewarming durations and neurological outcomes.

Group	Indication time (minutes)	Hypothermia time (hours)	Rewarming time (days)	Neurological outcome
Whole-body cooling	182.8±68.7*	39.7±8.7*	3.57±1.3*	GR: 4 MD: 2 SD: 1
Selective head cooling	256.7±67.5	36.7±9.8	1.87±2.1	GR: 4 MD: 3 SD: 1

Data are expressed as means ±S.D. * A significant difference was observed between the groups with the Mann-Whitney U-test ($P<0.05$). GR – good recovery; MD – moderately disabled; SD – severely disabled.

Table 3. Urinary 8-OHdG levels.

Group	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Whole-body cooling	5.89±4.00 (6.11)	6.68±5.78 (5.12)	9.01±7.17 (7.35)	9.36±6.97 (5.99)	6.02±6.60 (2.75**)	5.33±5.90 (2.45)*,**	4.92±5.20 (2.10)*,**
Selective head cooling	8.45±7.72 (7.43)	12.98±9.60 (10.30)	11.10±7.30 (10.90)	11.10±7.12 (7.12)	9.98±6.36 (8.00)	12.00±6.96 (11.20)	9.13±5.27 (7.68)

Data are expressed as means ±S.D. * A significant difference was observed between the groups with the Mann-Whitney U-test ($P<0.05$).
** A significant difference was observed compared with the data on day 1 in the whole-body cooling group by Friedman's χ^2 test ($P<0.05$).

Results

Table 1 shows the patient characteristics. The GCS scores at the start of hypothermia therapy were 5.6±1.6 in the whole-body cooling group and 5.8±2.1 in the selective head-cooling group. The Acute Physiology and Chronic Health Enquiry (APACHE II) scores were 17.9±3.7 in the whole-body cooling group and 15.5±2.6 in the selective head-cooling group. No significant differences were observed in either GCS or APACHE II scores between the groups. The patients in the whole-body cooling group (age, 40.3±6.7 years) were significantly younger than those in the selective head-cooling group (age, 52.8±4.7 years) ($p<0.05$) (Table 1).

Duration of induction and rewarming times

The induction duration in the whole-body cooling group (183±68 min) was significantly shorter than that in the selective head-cooling group (257±68 min) ($p<0.05$). The rewarming duration in the whole-body cooling group (3.57±1.3 days) was significantly longer than that in the selective head-cooling group (1.87±0.8 days) ($p<0.05$). The durations of hypothermic maintenance were 39±9 h in the whole-body cooling group and 37±10 h in the selective head-cooling group, and no significant differences were observed between the groups (Table 2).

Neurological outcomes

The neurological outcomes in patients 28 days after ICU admission were as follows: good recovery (GR) in 4, moderately disabled (MD) in 2 and severely disabled (SD) in 1 in the whole-body cooling group; GR in 4, MD in 3 and SD in 1 in the selective head-cooling group. The difference between these results was not significantly different (Table 2).

Changes in the levels of urinary 8-OHdG over 1 week

The levels of urinary 8-OHdG significantly decreased on days 6 and 7 compared with the levels on day 1 (before the start of hypothermia therapy) in the whole-body cooling group ($p<0.05$). No significant change was observed in the selective head-cooling group. In the whole-body cooling group, we observed significantly lower urinary 8-OHdG levels than the levels in the selective head-cooling group on days 5, 6 and 7 ($p<0.05$) (Table 3).

Discussion

We set out to examine the changes in the levels of urinary 8-OHdG during brain hypothermia therapy, and to compare 8-OHdG expressions in patients receiving whole-body cooling and in those receiving selective head cooling. Induced hypothermia was previously shown to improve the neurological outcome of unconscious survivors of out-of-hospital CA due to VF [11,12]. The ILCOR guidelines recommend that unconscious adult patients with spontaneous circulation after out-of-hospital CA should be cooled to 32°C for 12 to 24 hours if their initial cardiac rhythm shows VF; such cooling may be also beneficial for other types of cardiac rhythms, or in-hospital CA cases [9]. Moreover, the American Heart Association guidelines for cardiopulmonary resuscitation (CPR) of 2005 also recommend this treatment. Ala et al. reported that the early application of mild hypothermia with cold saline during prolonged CPR promotes survival in animal models [13]. Maturo et al. briefly addressed the possibility of the benefits of hypothermia to improve outcome after other types of CA [14]. Following these studies, we speculated that mild hypothermia might be beneficial for achieving neuroprotection after CA, not only in cases of VF but also in those of VT and PEA, even in hospital.

It is considered that full recovery from primary brain injury is difficult, and therefore the target of ICU management is neuroprotection from secondary brain damage caused by brain ischemia. Neurons in the brain tissue consume more oxygen than cells in other parts of the body, and are much more sensitive to hypoxia than other cells [15]. It is very important to start hypothermia therapy as soon as possible after brain ischemia. We chose selective head cooling in order to enable the immediate initiation of hypothermia therapy after CA in cases of patients with low blood pressure, or in those requiring repeated VT or VF for neuroprotection.

However, induced brain hypothermia with whole-body cooling using a cooling blanket may cause complications such as hypotension, arrhythmia, an increase in infection risk and a decrease in platelet count [5]. One of the most serious complications of brain hypothermia is uncontrollable hyperglycemia with glucose levels above 230 mg/dl, which has a high risk of systemic infections. In particular, pulmonary infection is a serious complication of hypothermia therapy [15]. In the current study, we managed hyperglycemia with sliding insulin therapy.

Recently, many articles reported several simplified management techniques for inducing brain hypothermia with a low risk of complications [16]. Dohi et al. reported that brain cooling with nasopharyngeal cooling produced good outcomes. This method involves inserting a catheter into the nasopharyngeal space and infusing cold air, which directly cools the basal part of the brain [17]. Furthermore, they reported that pharmacological brain cooling with indomethacin had good outcomes and reduced vasospasm occurrence in patients with a subarachnoid hemorrhage [18]. Ikeda et al. reported that non-steroidal anti-inflammatory drugs had direct superoxide-scavenging activity. These drugs may also be effective in patients with global ischemia [19]. Recently, several studies reported that intravascular hypothermia methods such as the use of the Celsius Control System (Intercool Therapies Ltd., Tokyo, Japan) induced brain hypothermia effectively and rapidly. This device, developed in 2004, is a cooling system which uses a femoral intravenous catheter to effectively and rapidly reduce and maintain target temperatures [20]. Nagao et al. showed that cardiopulmonary resuscitation using cardiopulmonary bypass with mild hypothermia may improve outcomes in patients who suffer out-of-hospital CA [21-23].

Barry et al. also reported successful and rapid selective brain cooling by surface cooling in an animal infant model of CA and resuscitation without changing core temperatures and with minimum adverse effects [6]. Human et al. reported rapid and selective cerebral hypothermia using a cooling helmet for patients with a head injury. In the present study, the patients required an average of 3 to 4 hours to achieve brain temperatures lower than 34°C [7]. We speculated that this method might be effective for patients following CA with circulatory instability or other complications such as severe pneumonia or bleeding. We also thought that this method might not require much sedation.

In this study, we performed selective head cooling with circulatory stabilization without strong sedation. Sedatives can have a strong effect on circulation and body temperature [24]. One of the most important benefits of selective head cooling is that it does not require strong sedation. In the present study, there were no major complications.

However, in the clinical setting, selective head cooling could not control bladder temperature and it took about 3 hours to reduce the tympanic membrane temperature. On the other hand, the rewarming procedure for this method was very simple and obtained good outcomes, similar to the outcomes of whole-body cooling in the present study. Moreover, we were able to maintain circulatory stability in the selective head-cooling group.

Induced brain hypothermia provides many neuroprotective functions such as decreasing intracranial pressure and brain edema, and the suppression of the production of glutamine, free radicals, nitrous oxide and inflammatory cytokines [5]. Kawai et al. reported that the neuroprotective mechanisms of postischemic hypothermia may be mediated by the suppression of leukocyte-mediated inflammation after ischemia and reperfusion [25,26]. Ohtaki et al. reported that interleukin-1 may have a role in brain ischemia. Free radicals stimulate the release of cytokines, and cytokines in turn induce the release of free radicals after brain ischemia [27]. Doi et al. reported that the expression of peroxynitrite and caspase-3 increased after ischemia and reperfusion in mouse CA models, and induced apoptosis of the brain cells associated with the generation of free radicals [28]. Mordecai et al. reported that post-traumatic hypothermia reduced glutamate and free radical production following brain injury [29].

Oxygen free radicals play important roles in the development of global brain ischemia after CA, and one of the most important effects of brain-induced hypothermia treatment is the suppression of free radical generation. Hashimoto et al. reported that selective brain-induced hypothermia reduced hydroxyl radical production against hypoxic-ischemic injury in newborn rats [30]. Mihara et al. showed that the production of serum radicals decreased during hypothermia therapy and increased in the rewarming phase in patients following CA [31]. Michael et al. reported that increased plasma peroxides are markers of oxidative stress in myalgic encephalomyelitis and chronic fatigue syndrome [32].

8-OHdG, which is produced by oxidative DNA damage, is one of the predominant forms of radical-induced DNA damage and has been widely used as a biomarker of oxidative stress [8]. The average level of 8-OHdG in humans is about 4.12 ng/ml [33,34]. Zhao et al. reported that urinary 8-OHdG and 8-iPGF indicated the occurrence of cerebral ischemia due to vasospasm following subarachnoid hemorrhage [35]. Following these studies, we speculated that urinary 8-OHdG might be a useful indicator of cerebral ischemia after CA. We chose this parameter as an oxidative stress marker because it does not involve an invasive procedure and is easy to monitor in the ICU.

In the present study, we observed significant decreases in the levels of urinary 8-OHdG after the rewarming phase in the whole-body cooling group, and these decreases were more suppressed in this group than in the selective head-cooling group. Naturally, urinary 8-OHdG may have been affected by the sedatives or anesthesia. It is of great interest that the levels of urinary 8-OHdG still decreased in the rewarming phase in the whole-body cooling group. Unfortunately, we could not clarify the underlying mechanism in the present study. In the selective head-cooling group, no significant change was observed after 1 week, and the levels of urinary 8-OHdG were not very high, that is, about twice that of healthy humans. On days 1-4, no significant differences were observed between the groups, and neurological outcomes were similar in both groups. Consistent with the findings of a previous study, which demonstrated the importance of preventing secondary brain damage after brain ischemia, the current results also showed that mild hypothermia therapy can decrease secondary brain damage and yield good outcomes in neuroprotection [15].

There are some limitations in the current study. In particular, we only studied a small group of patients at a single institution. However, these preliminary results show that mild hypothermia therapy with selective head cooling was effective in patients with circulatory instability after resuscitation. Furthermore, we believe that a combination therapy of whole-body cooling and selective head cooling after CA may also be effective. We speculate that this combination treatment might be easy to manage as a form of brain hypothermia therapy, particularly in the rewarming phase, where selective head cooling is maintained after the cessation of whole-body cooling.

Conclusions

Mild hypothermia therapy suppressed the levels of urinary 8-OHdG following global brain ischemia. Whole-body cooling showed a stronger suppression of the generation of free radicals than selective head cooling. We believe that selective head cooling is beneficial for patients with circulatory instability after resuscitation because it provides neuroprotection similar to that of whole-body cooling.

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