Application of hypothermia in neurological disorders: Simple yet effective head and neck cooling without sedation.

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Key words: Brain, hypothermia, cooling, volunteers, neurological disorders, brain injury, seizures, stroke, trauma, multiple sclerosis.

Running title: **Non-invasive cooling of the brain**

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Abstract

The therapeutic potential of hypothermia for various neurological disorders has been well established. However, direct cooling of the brain is not practical since it requires an invasive approach with sedation and/or anesthesia. We evaluated a non-invasive head-neck cooling system (CoolSystems Inc., Lincoln, CA) in 10 normal volunteers using an intestinal temperature sensor capsule (HQT Inc., Palmetto, FL), swallowed 5 hours before cooling, for measuring core temperature. All participants completed all of the cooling sessions without interruption or significant complaints. Thirty minutes of cooling produced a mean scalp temperature reduction of 12.4 C and a mean tympanic temperature reduction of 1.09 C. At the end of cooling, the mean core temperature was decreased by 0.06 C. At the end of 60 minutes of cooling, scalp temperature fell an average of 12.2 C, and ear temperature 1.67 C. The mean core temperature was decreased by 0.12 C. The difference between the beginning and end of cooling was statistically significant for scalp temperature ($p < 0.0001$) and tympanic temperature (right $p < 0.0001$, left $p < 0.0003$), but not for core temperature ($p = 0.2166$). This is the first study to show the feasibility and safety of head-neck cooling in conscious normal volunteers without causing shivering. An ongoing pilot study should reveal if this degree of change in core temperature as measured in the intestine has the potential for treating seizures.

Key words: Brain, hypothermia, injury, multiple sclerosis, seizures, stroke, trauma.

Introduction

Application of brain hypothermia has been found to be beneficial in various neurological conditions (Giesbrecht, 2000) such as traumatic brain injury (Polderman et al., 2004; Fritz & Bauer, 2004), stroke (Olsen et al., 2003; The ATLANTIS, ECASS, and NINDS rt-PA Study Group Investigators, 2004), and seizures (Ommaya & Baldwin, 1963; Vastola et al., 1969; Yang & Rothman, 2001). However, brain cooling is usually performed under sedation or general anesthesia using either a cooling blanket (Vastola et al., 1969) or surgical procedure (Bakken et al., 2003), thus precluding its routine use. If effective cooling of the brain could be accomplished routinely, or in an emergency situation where rapid and efficient intervention is critical, significant therapeutic improvements could be attained (Holzer et al., 2005). For example, in acute stroke, secondary injury could be decreased or prevented (Olsen et al., 2003) or the window for successful thrombolytic therapy could be extended (The ATLANTIS, ECASS, and NINDS rt-PA Study Group Investigators, 2004). In traumatic brain injury, posttraumatic recovery could be facilitated (Polderman et al., 2004; Fritz & Bauer, 2004), and in epilepsy, seizures could be terminated and neuronal injury decreased or prevented (Ommaya & Baldwin, 1963; Vastola et al., 1969; Yang & Rothman, 2001).

This article describes for the first time the feasibility and safety of non-invasive head and neck cooling without sedation in conscious normal volunteers without causing shivering.

Methods

We studied 10 normal volunteers (age 21-47 years, 5 males and 5 females) (table 1), each of whom underwent two cooling sessions (30 and 60 minutes) 3 days apart. During each session, temperature was measured every 5 minutes from the scalp, forearm, abdomen, and leg using a temperature transducer (Biolog, UFI, Morro Bay, CA), from both ears (Braun PRO 3000 Thermometer, Braun GmbH, Germany), and from the face and mouth using a hand-held infrared thermometer (D160 Infrared Thermometer Made In Japan, Addison, IL). Intestinal temperature was also measured using a temperature sensor pill 30 minutes before cooling, during each cooling and 30 minutes after cooling. The temperature sensor pill (HQ, Inc., Palmetto, FL) was swallowed 5-6 hours prior to the onset of cooling. Peripheral oxygen saturation and pulse rates were monitored with a pulse oxymeter. Each subject was comfortably seated in a reclining chair and covered with blankets to keep the body warm during cooling.

We used the same cooling helmet as Wang et al. (2004) in their study of 8 patients with severe stroke or head injury. This two- component head-neck cooling system (CoolSystems, Inc., Lincoln, CA), a product originally of NASA engineering and invented by one of the co-authors (WE), was built as a prototype head-neck cooling system for patients with multiple sclerosis (Ku et al., 1996). It includes a head/neck liner made of a lightweight thin flexible laminated nylon urethane fabric, and a conditioning unit (temperature Control, liquid pump and pressure control, air pump). We used the lowest temperature the cooling device could produce. The cooling headgear was applied 30 minutes before cooling started and removed at the end of cooling. The t-test was used to compare temperature before and after cooling.

Results

Output temperature of the cooling system at the beginning of cooling was approximately 1.5°C, the maximum temperature the system can produce, and rose to approximately 4.5-5°C at the end of cooling. Just before cooling began, the average scalp temperature was 34.1°C, the right ear 36.6°C, the left ear 36.5°C, and core temperature 37.1°C.

Table 1 shows the change in temperature from baseline to the end of each cooling period.

The overall mean reduction of core temperature at the end of 30 minutes of cooling was 0.06°C, and at the end of 60 minutes of cooling, 0.12°C.

A statistically significant difference was seen between the beginning and end of cooling in both scalp temperature ($p < 0.0001$) and tympanic temperature (right ear $p<0.0001$, left ear $p<0.0003$), but not in core temperature ($p=0.2166$). There was no statistical difference between men and women in degrees of temperature changes except for scalp temperature at the end of the 60-minute cooling periods ($p=0.0235$).

Temperatures from other areas (arm, abdomen, and leg) were unchanged throughout the cooling periods of both 30 and 60 minutes, as were the measurements of heart rates and oxygen saturation rates.

Figure 1a shows temperature changes before, during and after 60 minutes of cooling in a 27 year-old man, and 1b shows an expanded display of changes in core temperature. All volunteers remained mentally alert and coherent throughout the duration of the cooling periods.

Discomforts during cooling included a mild “ice cream” headache (1), mild nausea (1), a mild headache and nauseated feeling (1), and a “chilly sensation” (1). No interruption of cooling, however, was necessary in any of these cases. One female subject awakened with a mild headache on the morning of the cooling experiment, but reported alleviation of her headache during the cooling session.

Discussion

This is the first study to show the feasibility and safety of head-neck cooling in conscious normal volunteers without causing shivering. Even though the output temperature from the cooling system was significantly lower (1.1 -1.7 °C) in our study than in a recent MS study (12.7°C) (NASA/MS Cooling Study Group., 2003), no significant side effects requiring discontinuation of cooling were encountered. The most important element was to keep the torso warm during cooling to prevent the occurrence of shivering. We found that cooling efficacy seemed to depend on the fitness of the headgear and amount of hair. For example, a 35-year old man whose hair was very short and whose cooling helmet fit exceptionally well had the lowest core temperature after 30 minutes of cooling and the second lowest after 60 minutes of cooling.

The neuroprotective properties of hypothermia are strongly implied (Holzer et al., 2005), but it is not yet completely understood at what level or to what extent hypothermia can be beneficial (Giesbrecht, 2000). Furthermore, clinical and experimental evidence suggests that hyperthermia decreases seizure threshold (Ommaya & Baldwin, 1963; Vastola et al., 1969) and experimental data demonstrate that cooling of the cortex changes its electrical behavior (Vastola et al., 1969; Sourek & Travnicek, 1970; Hill et al., 2000; Yang & Rothman, 2001; Yang et al., 2002) and may stop seizures (Ommaya & Baldwin, 1963; Vastola et al., 1969; Yang & Rothman, 2001; Yang et al., 2002).

Invasive animal data indicate that hypothermia induces changes in the ionic environment affecting synaptic transmission in the hamster hippocampus (Igelmund & Heinemann, 1995), improves cortical excitability after ischemic injury in the rat (Sick et al., 1999), decreases brain damage following neonatal hypoxic-ischemic seizures in rats (Yager et al., 2004), attenuates NO production during drug-induced seizures and decreases CA3 hippocampal brain lesions in the immature rabbit brain (Takei et al., 2004), protects hippocamal cultures (Feiner et al., 2005), and suppresses EEG during treatment while decreasing mortality following severe cortical injury in rats (Clark et al., 1996). Hypothermia was even effective in stopping experimental seizures in rats (Yang & Rothman, 2001). A non-invasive study similar to ours was performed on newborn swine (Laptook et al., 2001) by cooling the top of the head with circulating ice water in inflatable cuffs. A modest lowering of brain temperature (~1 °C), but no significant lowering in rectal temperature was noted during 70-80 minutes of cooling.

A novel surface cooling method using a cold pad applied over a large skin surface was tried in normal subjects, who, however, were medicated to prevent shivering (Zweifler et al., 2001). In this report, core temperature was determined by tympanic temperature, and it took approximately 77 minutes to achieve the core temperature of 35ºC and about 119 minutes to obtain the core temperature of 34º C. Previously, cooling of patients was performed with craniotomy or under general anesthesia to treat, for example, severe epileptic seizures (Sourek & Travnicek, 1970). Progress towards the non-invasive application of hypothermia was recently reported by Wang et al. (2004) who treated patients with severe stroke or brain injury. However, these patients were sedated or anesthetized and brain temperature was monitored invasively using an intracerebral temperature sensor. An average reduction of 1.84°C (range 0.9-2.4°C) was seen within 1 hour of applying the cooling helmet, with a significant drop within 15 minutes in some patients. Interestingly, no such change was seen in core temperature (bladder) for a long period of time even though each patient's head was shaved. Thus, it is reasonable to speculate that brain temperature in the normal volunteers in our study might have been significantly lower than the core temperature suggested.

The optimal measure of core temperature remains unknown. The question also remains as to whether or not a statistically significant change in core temperature measured outside of the cranium is required to achieve a therapeutic effect (Jessen, 2001). Further study in patients is necessary to optimize the cooling procedure.

Head-neck cooling using CoolSystems' cooling device is feasible and safe. Cooling up to 60 minutes without sedation was well tolerated by normal volunteers, and discomforts were minimal. This cooling method can easily be applied to patients who require rapid intervention.

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