HYPOTHERMIA AS MEDICAL TREATMENT.

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Introduction:

Therapeutic hypothermia**,** now also known as targeted temperature management is a treatment method which is able to reduce mortality of successfully resuscitated cardiac arrest victims by subjecting them to lower their core body temperature.

There exists a growing body of evidence that hypothermia increases survival chances and quality for patients suffering from other ischemic insults such as stroke or generalized brain trauma. It can also be used to manage fever in patients suffering neurological injuries.

History

This technique has been described in various times in the history of medicine. Hippocrates, recommended the packing of wounded soldiers in snow and ice.[1] Napoleonic surgeon Baron Dominque Larrey recorded that officers, who were kept closer to the fire, survived less often than the minimally pampered infantrymen[1]. In modern times the first medical article concerning hypothermia was published in 1945.[1] This study focused on the effects of hypothermia on patients suffering from severe head injury. In the 1950's hypothermia received its first medical application, being used in intracerebal aneurysm surgery to create a bloodless field. [1] Most of the early research focused on the applications of deep hypothermia, defined as a body temperature between 20-25 °C (68-77 °F). Such an extreme drop in body temperature brings with it a whole host of side effects, side effects which made the use of deep hypothermia impractical in most clinical situations. This period also saw sporadic investigation of more mild forms of hypothermia, with mild hypothermia being defined as a body temperature between 32-34°C (89.6-93.2°F). In the 1950's Doctor Rosomoff demonstrated in dogs the positive effects of mild hypothermia after brain ischemia and traumatic brain injury.[1] In the 1980's further animal studies indicated the ability of mild hypothermia to act as a general neuroprotectant following a blockage of blood flow to the brain. This animal data was supported by two landmark human studies published simultaneously in 2002 by the New England Journal of Medicine. Both studies, one occurring in Europe and the other in Australia, demonstrated the positive effects of mild hypothermia applied following cardiac arrest.[2] In 2003 the American Heart Association (AHA) and the International Liaison Committee on Resuscitation (ILCOR) endorsed the use of therapeutic hypothermia following cardiac arrest.[3] Currently, a growing percentage of hospitals around the world incorporate the AHA/ILCOR guidelines and include hypothermic therapies in their standard package of care for patients suffering from cardiac arrest. Some researchers go so far as to contend that hypothermia represents a better neuroprotectant following a blockage of blood to the brain than any known drug.[4]

Types of ischemic events

The types of medical events hypothermic therapies may effectively treat fall into three primary categories: cardiac arrest, ischemic stroke, and neurogenic fever following brain trauma.

Cardiac arrest

The data concerning hypothermia's neuroprotectant qualities following cardiac arrest can be best summarized by two studies published in the New England Journal Medicine. The first of these studies conducted in Europe focused on people who were resuscitated 5-15 minutes after collapse. Patients participating in this study experienced spontaneous return of circulation (ROSC) after an average of 105 minutes. Subjects were then cooled over a 24 hour period, with a target temperature of 32-34°C (89.6-93.2°F). 55% of the 137 patients in the hypothermia group experienced favorable outcomes, compared with

only 39% in the group that received standard care following resuscitation.[2] Death rates in the hypothermia group were 14% lower, meaning that for every 7 patients treated one life was saved.[2] Notably, complications between the two groups did not differ substantially. This data was supported by another similarly run study that took place simultaneously in Australia. In this study 49% of the patients treated with hypothermia following cardiac arrest experienced good outcomes, compared to only 26% of those who received standard care.[5]

Stroke

Most of the data concerning hypothermia's effectiveness in treating stroke is limited to animal studies. These studies have focused primarily on ischemic as opposed to hemorrhagic stroke, as hypothermia is associated with a lower clotting threshold. In these animal studies, hypothermia represented an effective all purpose neuroprotectant.[6] This promising data has lead to the initiation of human studies. Unfortunately, at the time of this article's publishing, no results have yet been returned. In terms of feasibility, however, the use of hypothermia to control intracranial pressure (ICP) after an ischemic stroke was found to be both safe and practical.[7] In 2008, long-term hypothermia induced by low-dose hydrogen sulfide, a weak, reversible inhibitor of oxidative phosphorylation, was shown to reduce the extent of brain damage caused by ischemic stroke in rats.[8]

Fever

The effects of elevated body temperature following cardiac arrest, stroke, and brain trauma are surprisingly pronounced. According to one study, elevated body temperature correlated strongly with an extended stay in the ICU for patients suffering from either brain ischemia or brain trauma.[9] Another paper stated that those suffering from either brain trauma or brain ischemia that entered the ICU with a fever had a 14% higher mortality rate than normothermic patients.[10] It appears that the ischemic or traumatized brain is particularly susceptible to the damaging influence of elevated temperature. Combating fever through the use of temperature dampening devices represents a critical aspect of neurological care.[11]

Cellular mechanism

Faced with this extensive array of clinical data, many scientists have attempted to explain the cellular processes responsible for the therapeutic effect of hypothermia following a blockage of blood flow to the brain. The earliest explanations for why hypothermia acted as a neuroprotectant focused on the slowing of cellular metabolism resultant from a drop in body temperature. For every drop in body temperature of a degree Celsius cellular metabolism slows by 5-7%.[10] Because of this reality, most early theorists believed that hypothermia lessened the harmful effects of oxygen deprivation by decreasing the body's need for oxygen.[1] The initial emphasis on cellular metabolism explains why the early studies almost exclusively focused on the application of deep hypothermia, as these researchers believed that the therapeutic effects of hypothermia correlated directly with the extent of temperature decline.[12]

One of the most promising explanations centers on the series of reactions that occur following oxygen deprivation, particularly those concerning ion homeostasis. In truth, cell death is not caused by oxygen deprivation directly, but rather the cascade of reactions that oxygen deprivation leads to. Cells need oxygen to create ATP--a molecule used by cells to store energy--and cells need ATP to regulate cellular ion levels. Simply, cells use ATP to fuel both the importation of ions necessary for cellular function and the removal of ions that are harmful to cellular function. Without oxygen, cells cannot manufacture the necessary ATP to regulate ion levels and thus cannot prevent the intercellular environment from approaching the ion concentration of the outside environment. It is not oxygen deprivation itself that precipitates cell death, but rather the disruption of homeostasis resultant from oxygen deprivation that leads to cellular apoptosis.[1]

It is seen that even a small drop in temperature encourages cell membrane stability during periods of oxygen deprivation. For this reason, a drop in body temperature helps prevent an influx of unwanted ions during an ischemic insult. By making the cell membrane more impermeable, hypothermia helps prevent the cascade of reactions set off by oxygen deprivation. Even moderate dips in temperature strengthen the

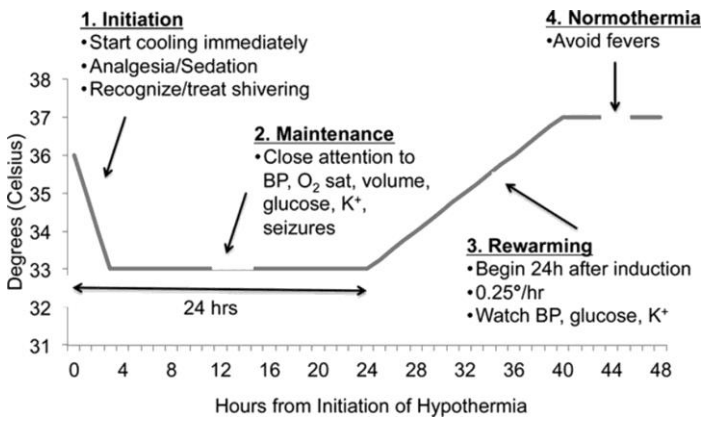
cellular membrane, helping to minimize any disruption to the cellular environment. It is by moderating the disruption of homeostasis caused by a blockage of blood flow that many now postulate results in hypothermia's ability to minimize the trauma resultant from ischemic injuries.[1]

The therapeutic effect of hypothermia does not confine itself to metabolism and membrane stability. Another school of thought focuses on hypothermia's ability to prevent the injuries that occur after circulation returns to the brain, or what is termed reperfusion injuries. An individual suffering from an ischemic insult continues suffering injuries well after circulation is restored. In rats it has been shown that neurons often die a full 24 hours after blood flow returns.[13] Some theorize that this delayed reaction derives from the various inflammatory immune responses that occur during reperfusion. These inflammatory responses cause intracranial pressure, pressure which leads to cell injury and in some situations cell death. Hypothermia has been shown to help moderate intracranial pressure and therefore to minimize the harmful effect of a patient's inflammatory immune responses during reperfusion. Beyond this, reperfusion also increases free radical production. Many now suspect it is because hypothermia reduces both intracranial pressure and free radical production that hypothermia improves patient outcome following a blockage of blood flow to the brain.[1]

Mechanics

It is important to note the various clinical realities associated with this medical procedure. The animal data suggests that the earlier hypothermia is induced the better the subject's outcome.[13] However, therapeutic hypothermia remains partially effective even when initiated as long as 6 hours after collapse.[14] Patients entering a state of induced hypothermia should also receive extensive monitoring. Clinicians must remain watchful of the negative side-effects associated with hypothermia. These side-effects include: arrhythmia, decreased clotting threshold, increased risk of infection, and electrolyte imbalance. The medical data suggests that these side-effects can be mitigated only if the proper protocols are followed. We must avoid overshooting the target temperature, as hypothermia's negative side-effects increase in severity the lower a patient's body temperature drops.[14] The accepted medical standards indicate that a patient's temperature should not fall below a threshold of 32°C (89.6°F).[14]

Medical professionals must attempt to minimize a patient's shivering response. For human beings temperature represents one of our most tightly regulated parameters.[4] When body temperature drops below a certain threshold--typically around 36 °C (96.8 °F) --patients will begin to shiver.[4] It appears that regardless of the technique used to induce hypothermia, patients begin to shiver when temperature drops below this threshold.[4] This behavior hinders the ability of medical professionals to induce hypothermia. For this reason, hypothermia should be induced in conjunction with pharmaceuticals that prevent this reaction. Finally, clinicians should rewarm patients slowly and steadily in order to avoid unhealthy spikes in intracranial pressure.[14] A patient's rewarming should occur at a rate of .5-1 °C an hour in order to avoid injury. In fact, most deaths caused by therapeutic hypothermia occurred during the rewarming phase of the procedure, deaths easily avoided by slow and precise rewarming.[15]



Methods

Cooling catheters

Cooling catheters control temperature through invasive internal methods. The process works by inserting a catheter into the femoral vein in the IVC. Once the catheter is introduced, a control unit governs the temperature of saline solution circulating through either a metal coated tube or a balloon. The saline cools the patient's whole body

by lowering the temperature of a patient's blood as it leaves the heart. The main advantage of catheters over other cooling alternatives is their precision and speed. Catheters reduce temperature at rates approaching 4 °C per hour. Through the use of the sophisticated control unit, catheters can bring body temperature to within.1 °C of the target level. This level of accuracy allows doctors to avoid many of the pitfalls associated with excessively deep levels of hypothermia. Furthermore, catheters can raise temperature at steady rate, which helps to avoid harmful rises in intracranial pressure

This invasive technique has been associated with bleeding, infection, vascular puncture, and deep vein thrombosis.[16] Infection caused by cooling catheters is particularly harmful, as resuscitated patients are highly vulnerable to the complications associated with infections. [17] Bleeding too represents a significant danger to patients, due to a decreased clotting threshold caused by hypothermia. The risk of deep vein thrombosis might be the most pressing medical complication. One study found that incidents of deep vein thrombosis increased by 33% if a patient's catheter was kept active for 4 days or less and 75% if their catheter was left attached for 4 days or more.[18]

Non-invasive

Water blankets

Water blankets are a technology where cold water circulates through a blanket using positive pressure. To lower temperature with optimal speed, medical professionals must cover 80% of a patient's surface area with water blankets. These blankets are typically augmented by ice packs or cold fans in order to achieve more rapid temperature decline. This technique of temperature management dates back to the 1950's and represents perhaps the most well studied means of controlling body temperature. Water blankets lower a patient's temperature exclusively by cooling a patient's skin and accordingly require no insertion of anything into the patient's body. Furthermore, nursing professionals can administer water blankets without a supervising M.D.

Water blankets possess several undesirable qualities. First off, they are particularly susceptible to leaking and for this reason represent a serious electrical hazard. Also, water blankets are labor intensive and require near constant monitoring.[21] Water blankets were not designed with sophisticated temperature management in mind and applying water blankets for this purpose requires large amounts of effort on the part of hospital staff. In addition to the labor required, water blankets lower body temperature at a slower rate than other cooling alternatives. Most machines now come with core temperature probes. When inserted into the rectum of the patient, the core body temperature can be monitored. The water blanket can then be adjusted to the desired temperature set by the healthcare provider that, in return, allows for a more accurate temperature range. Also, water blankets can cool patients less precisely than alternative methods. Water blankets tend to overshoot the target temperature and cool patients to levels below 32 °C (89.6 °F). Due to their imprecision, water blankets often can overcool patients leading to risks or may rewarm patients at too quick a rate. This leads to spikes in intracranial pressure, spikes that can cause serious brain injury and in some instances patient mortality.

Conclusion:

The use of hypothermia for therapeutic purposes represents a technique with increasing levels of application. Virtually unrecognized until recent years, it is now part of the standard of care for the thousands of individuals suffering from cardiac arrest every year. It is being continually explored and optimized and has good future in application of neuroprotection and may show promising outcomes on long term studies in cardiac and renal protection as well.

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