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Neurologic Outcome after Cardiac Arrest with the Use of Mild Therapeutic Hypothermia

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Mild Therapeutic Hypothermia to Improve the Neurologic Outcome After Cardiac Arrest

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Treatment of Comatose Survivors of Out-of-Hospital Cardiac Arrest with Induced Hypothermia

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Aim of these studies

The purpose of these studies was to evaluate the benefits of induced hypothermia in the neurologic outcome of patients suffering a cardiac arrest.

Methods

In the Austrian study, the criteria for inclusion were: a witnessed cardiac arrest, ventricular fibrillation as the initial cardiac rhythm, a presumed cardiac origin of the arrest, an age of 18 to 75 years, an estimated interval of 5 to 15 minutes from the patient's collapse to the first attempt of resuscitation by emergency medical personnel and an interval of no more than 60 minutes from collapse to return of spontaneous circulation (ROSC).

In the Australian clinical trial, the criteria for inclusion were: ventricular fibrillation as the initial cardiac rhythm, successful ROSC, persistent coma after the ROSC, and transfer to one of the four participating emergency departments.

Treatment, Protocols and Randomization

In the Australian clinical trial, there were a total of

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77 patients, of which 43 were assigned to hypothermia and 34 to normothermia. The hypothermia group reached a core temperature of 33°C with ice packs applied around the head, neck, torso and limbs, 2 hours after the ROSC and maintained for 12 hours.

In the European clinical trial, 275 patients were enrolled, with 137 randomly assigned to the hypothermia group and 138 to the normothermia group. The hypothermia group reached the target core temperature of 32°C to 34°C with the use of a mattress with a cover that delivered cold air over the entire body within 4 hours of ROSC and maintained for 24 hours. If this temperature was not archieved, then ice packs were applied.

Results

In the Australian study, 49 percent of the patients treated with hypothermia survived and had a good outcome (were discharged home or to a rehabilitation facility) as compared with 26 percent of those with normothermia (P=0.046). There was no difference in the frequency of mortality or adverse events between the two groups.

In the Austrian study, 55 percent of patients in the hypothermia group had a favorable neurologic outcome (sufficient cerebral function to live independently and work at least part-time) as compared to 39 percent in the normothermia group. There was no difference in the frequency of mortality or complications between the two groups.

Conclusion

Therapeutic hypothermia in these studies increased the rate of a favorable neurologic outcome and reduced mortality in victims of cardiac arrest.

Commentary

It is important to point out that induced hypothermia may not benefit all patients who have survived a cardiac arrest. In both the studies presented, strict inclusion and exclusion criteria were used to select out that cohort of patients most likely to survive to hospital discharge. While the number of patients screened in the Australian study was not presented, only 7.7% of patients who suffered a cardiac arrest (and were screened) were enrolled in the Austrian study. Furthermore, the method of randomization in the Australian study is somewhat troubling. Patients were randomized to standard therapy or induced hypothermia according to the day of the month (odd or even days). The failure to conceal randomization may have had an impact on the aggressiveness of the patients pre-ICU care.

Induced hypothermia has been in use since the 1930´s when Dr. Temple Fay discovered the regression of malignant tumors in vitro [1,2]. Since the 1950´s there is evidence that induced hypothermia has benefits on patients with different diseases.

The rationale behind the use of this technique is related to the pathophysiology of cerebral ischemia. After a cardiac arrest anoxic neurologic injury is an important cause of mobility and mortality [3,4]. There is evidence that suggest that part of the neurologic injury occurs after the ROSC which causes a series of morphological and biochemical changes. Ischemia induces a decrease of cerebral oxygen delivery, which decreases ATP production, increases influx of calcium into cells (thought to be the major mechanism of injury) and increases the production of free radicals leading to membrane damage. The loss of membrane integrity causes further influx of calcium which is taken up by mitochondria after reoxygenation, inhibiting cellular enzymes, denaturing proteins and causing necrosis. Free radicals are generated from oxidative metabolism of arachidonic acid leading to a reduction of iron (Fe 3+) to soluble Fe 2+ causing lipid peroxidation, protein damage and DNA damage [5,6].

It has been shown that after ROSC, for 12 to 24 hours, the cerebral oxygen delivery may be decreased and the demand increased contributing to a continuing cerebral ischemia.5 During this time there is a massive increase in the intracellular concentration neurotransmitters such as glutamate and dopamine [7]. In addition to this, the cerebral edema and increased intracranial pressure promote ischemia [5,8].

Evidence shows that induced hypothermia has maximum benefit when it is applied immediately after ROSC. Yet a decrease in the neurologic injury is still observed 1 hour after the onset of ischemia [5,9]. In the 1950´s it was believed that the benefit of hypothermia was due to the reduction in oxygen requirements [10,11], but now it seems that it provides protection against the previously described biochemical mechanisms.