Medical Intelligece

Induced Hypothermia Following Cerebral Anoxia

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In 1958, Williams and Spencer reported on the use of total body hypothermia to treat cerebral edema secondary to cerebral anoxia which arose during cardiac arrest.¹ Their success with four patients led to a further clinical trial ² and to animal studies ³ both of which supported the value of hypothermia in this clinical situation. Since these early enthusiastic reports from one institution, only isolated case reports have appeared noting the successful use of hypothermia following severe cerebral anoxia. No other studies directed toward evaluating this therapy in patients have been published and interest seems to have waned. It is not clear whether the original work was not generally accepted or if accepted, was followed by disappointment from poor results which remain unreported. In view of the new information which has become available in the intervening years, a critical appraisal of the therapeutic value of hypothermia following cerebral damage seems appropriate.

In the original report of Williams and Spencer, 4 patients had cardiac arrest lasting 3–5 minutes and after resuscitation, suffered neurologic damage which the authors classified as severe. Hypothermia (30–34° C.) was induced immediately after resuscitation, and was maintained for 24–72 hours. All patients survived, 3 without neurological sequelae and one with moderate loss of vision.

Later, Benson and his associates ⁴ reported on 27 patients who were resuscitated from asystole or ventricular fibrillation. Immediately after resuscitation, 19 patients showed moderate or severe neurological damage judged by the degree of coma, convulsions and spasticity. Twelve of the 19 were treated promptly with hypothermia (31–32° C.) lasting from 3 hours to 8 days. Only one of the 7 without hypothermia survived whereas 6 of the 12 treated with hypothermia survived. Although this difference is impressive, the conclusions must be qualified. Since the degree of neurological damage was estimated immediately after resuscitation, it was impossible to know that patients in both groups suffered equivalent degrees of cerebral anoxia. In addition, the mean age of the survivors in the hypothermic group was 17.5 years compared to 45 years in the non-survivor hypothermic group and 49 years in the non-survivor normothermic group. There is considerable opinion and some data which suggest that at least the very young are more resistant than adults to cerebral damage resulting from hypoxia. ⁵ Finally, the incidence of hyperpyrexia following resuscitation in the normothermia group was not recorded. This is highly pertinent since a major question exists as to whether the value of hypothermia in this situation is not due entirely to the prevention of postanoxic hyperpyrexia. This question remains unanswered by any studies reviewed here.

Surprisingly, animal studies have not provided a clear answer either. Zimmerman and Spencer ⁶ developed a method of producing cerebral anoxia of precise duration in the dog. Complete arrest of the cerebral circulation for ten minutes was produced in 26 dogs, 14 of whom were treated with hypothermia (31–33° C.) for 18 to 36 hours. Of the 12 animals not treated, only 3 (25 per cent) survived and one of these suffered neurological damage. In the hypothermic group, 79 per cent of the animals survived long enough to demonstrate complete neurologic recovery, and 57 per cent ultimately survived. Unfortunately, temperature was not monitored in the control group and the contribution of hyperpyrexia to mortality is not known.

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Wolfe undertook a similar study in dogs but produced cerebral anoxia by inducing ventricular fibrillation. All 10 uncooled dogs died within 65 hours. Of the 10 dogs treated by immediate hypothermia (31°C) for 24 hours, three survived with no neurologic damage and the mean survival time of the hypothermic group was greater than that of the control. A similar study with a different outcome was carried out by Mullan, Raimondi and Suwanwela who produced asphyxia for 6 minutes in dogs. After resuscitation, 10 dogs were cooled to 28–30°C and allowed to rewarmed over 6–12 hours. Six of 10 cooled dogs and 7 of 10 uncooled dogs died 12–24 hours after asphyxia.

Since cerebral edema is assumed to follow mechanical brain trauma and to be benefited by hypothermia as well, a review of the data concerning the use of hypothermia after cerebral trauma may contribute some information on this problem. Drake and Jory treated 21 patients with severe head injury with hypothermia (28–36°C) for 2 to 10 days. All injuries were assumed to be potentially fatal (hyperpyrexia, deacrebrate rigidity and falling vital functions). Hypothermia was initiated 1 hour to 3 days after injury. There were 12 survivors, 6 of whom were permanent invalids with “dementia” and/or hemiplegia. Of the 9 deaths, 8 were due to staphylococcal pneumonia and one to gastrointestinal bleeding. The only factor common to the survivors was said to be youth but the ages were not listed. The authors pooled their data with those of two other studies in which patients with severe head injury were treated with hypothermia. The overall mortality rate in these 98 patients was greater than 50 per cent. Although 25 per cent of all patients recovered completely another 17 per cent were alive but totally incapacitated. In no study was there a control group for comparison.

As is the case with cerebral anoxia, animal studies of cerebral trauma have failed to provide a clear answer. Rosomoff and his co-workers produced cerebral injury in dogs by either ligation of middle cerebral artery or by the production of a standard cold injury to the brain. If either type of injury was inflicted after induction of total body hypothermia (22–24°C), there was significantly less disruption of the cyto-architecture of the brain, less severe neurological deficit on recovery and a lower mortality rate compared to normothermic animals. In further experiments, hypothermia was induced at varying periods after injury. With ligation of the middle cerebral artery the least cerebral damage and neurological deficit were observed when hypothermia was induced within fifteen minutes and body temperatures reached 22 to 24°C within 90 minutes. If hypothermia was delayed beyond 30 minutes after ligation, no differences from control in mortality or morbidity were observed. With cold injury, significant protection could be demonstrated if hypothermia (22–27°C) was induced up to three hours after injury. It is noteworthy that hypothermia increased survival time fivefold after cold injury but did not alter the ultimate mortality rate. In a similar experiment, Laskowski, Klatzo and Baldwin were unable to demonstrate any benefit from hypothermia initiated 6 hours after cold injury.

The benefits of hypothermia after spinal cord injury were recently demonstrated by Albin et al. After standard mechanical injury of the exposed spinal cord, deep hypothermia (12°C) was immediately induced but limited to the local area of injury and maintained for 2.5 hours. Although all uncooled dogs were paraplegic after 2 months, all 10 treated dogs recovered within 17 days with mild neurological defect in only 2 dogs.

In contrast to these reports, Mullen, Raimondi and Suwanwela found twice the mortality in dogs treated with hypothermia (29°C) 15 minutes after mechanical brain injury when compared to controls. In only one study was any consideration given to hyperpyrexia. Bouzarth et al. produced blast injury to the head in 225 dogs. In 97 dogs hypothermia to 31°C was induced immediately and maintained for 3 hours. In 95 dogs, normothermia was maintained for a similar period and in 33 dogs hyperpyrexia (41°C) was induced for 3 hours. Animals were not treated further and were sacrificed at intervals after injury. Surprisingly, there was no difference in mortality rate among the 3 groups. The only significant effects of treatment were that hypothermia decreased post-injury lethargy, but increased subdural bleed-
ing; hyperpyrexia did the opposite. The authors recommended maintenance of normo-
thermia after craniocebral trauma in patients.

To summarize these studies, the clinical reports are enthusiastic but inadequately con-
trolled and all ignored the possibility that the major benefit may have been derived from
prevention of post-traumatic hyperpyrexia. The animal studies also ignored this possi-
bility. The studies of cerebral trauma do not clearly demonstrate an improvement in mortal-
ity, even though survival time was prolonged. In the only study which considered hyper-
pyrexia, no difference in mortality between the hypothermic and hyperpyretic groups was
demonstrated.12

It is generally assumed that cerebral edema invariably follows cerebral anoxia and is the
cause of delayed or progressive brain damage after the initial anoxic insult. It is also
assumed that edema develops about local areas of brain trauma and causes additional cellular
damage and circulatory insufficiency. Hypothermia is assumed to exert its beneficial effect
by suppressing edema formation, in addition perhaps by decreasing the rate of oxygen con-
sumption and thereby increasing the survival of cellular elements. Harly13 recently re-
viewed the evidence used to support these assump-
tions and concluded that cerebral edema sufficient to produce clinically significant brain
swelling does not follow cerebral anoxia. He argued that a more likely cause of the delayed
or progressive symptoms after hypoxia was progressive damage to astrocytes and oligo-
dendrocytes which may then give rise to some edema of the white matter. Some of the re-
ports reviewed here clearly showed that the rate of development of glial damage can be
dramatically modified by hypothermia during and at times after injury.4, 9, 11 That the ultimate
degree of injury can be modified by hypothermia has not been so clearly shown.
The role of hypothermia in decreasing volume of the brain, cerebrospinal fluid pressure, cere-
bral blood flow and cerebral oxygen requirements is probably negligible in this response.
Some basis, although tenuous, therefore exists for anticipating a salutary effect of hypo-
thermia after brain anoxia or mechanical injury, apart from its role in preventing hyper-
pyrexia.

It is strange, therefore, that so few clinical reports of its use have appeared recently and
 casual inquiry fails to reveal very extensive use of hypothermia either after cerebral anoxia
or head injury. Hart14 in discussing the early management of head injuries has remarked,
"It is a somewhat surprising fact that in a major neurosurgical centre in this country,
hypothermia is not employed in the treatment of head injuries, while in another, earlier en-
thusiasm for its use has waned. The writer has never seen it used during some three years
at a large accident centre. Instead, normothermia, which protects the brain from the
harmful effects of hyperpyrexia, is preferred. The reason is that the marked clinical improve-
ment produced by cooling patients with brainstem damage, becomes apparent in the major-
ity of cases when the temperature has reached normal." Possibly the complications of the
prolonged hypothermia which has been used clinically, have discouraged clinicians. These
have included pneumonia, gastro-intestinal hemorrhage, cardiac arrhythmias, decreased
blood clotting and alterations in vital signs which increase the complexity of prolonged
nursing care.

Conclusion

It is clear that insufficient data exist on which a firm decision can be made as to the
value of hypothermia in treating brain injury. The needs in future studies include establish-
ment of criteria by which patients can be graded as to the severity of cerebral damage
prior to treatment, a balanced control group without hypothermia, application of a stand-
ard depth and duration of hypothermia and a specific interval after injury after which this
therapy would not be considered applicable. In view of its uncertain status and because the
therapy is not innocuous, it would seem wise at present to limit the use of hypothermia to
the prevention of hyperpyrexia following brain injury from any cause, and to maintain thereby
normothermia in the injured patient.

References

1. Williams, C. R., Jr., and Spencer, F. C.: The
clinical use of hypothermia following cardiac
INDUCED HYPOTHERMIA FOLLOWING CEREBRAL ANOxia


Drugs

**COBRA NEUROTOXIN** The neuromuscular blocking activity of cobra neurotoxin was studied electrophysiologically in rats and frogs. The purified neurotoxin component behaved similarly to *d*-tubocurarine. End plate potentials were decreased markedly as was the response to repetitive stimulation (Wedensky inhibition). No effect was noted on the terminal nerve spikes, action potentials of muscles or resting membrane potentials. Neurotoxin presynaptic activity is similar to curarine in that both block antidiromic activities of motor nerves in the presence of neostigmine. A component in the crude venom which travels electrophoretically with the cardio- toxic fraction has some depolarizing activity. This component, however, contributes only about 5 per cent of the total toxicity of the crude venom. These electrophysiological studies confirm earlier work which showed that cobra neurotoxin blocks neuromuscular transmission by its antidepolarizing action as evidenced by: (1) no inhibition of ACh production, (2) lack of effect on direct muscle stimulation, and (3) antagonism by neostigmine. (Chang, C. C., and Lee, C. Y.: Electrophysiological Study of Neuromuscular Blocking Action of Cobra Neurotoxin, Brit. J. Pharmacol. 28: 172 (Nov.) 1966.)