Combined application of hypothermia and medical gases in cerebrovascular diseases

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Abstract

Cerebrovascular diseases have a heavy burden on society and the family. At present, in the treatment of cerebrovascular diseases, the recognized effective treatment method is a thrombolytic therapy after cerebral infarction, but limited to the time window problem, many patients cannot benefit. Other treatments for cerebrovascular disease are still in the exploration stage. The study found that medical gas and hypothermia have brain protection effects. Further research found that when the two are used in combination, the therapeutic effect has a superimposed effect. This article reviews the current research progress of hypothermia therapy combined with medical gas therapy for cerebrovascular disease.

Key words: hypothermia therapy; medical gas; cerebrovascular diseases; neuroprotection; ischemic stroke; xenon; normobaric hyperoxia

doi: 10.4103/2045-9912.248269
How to cite this article: Li H, Tan X, Xue Q, Zhu JH, Chen G. Combined application of hypothermia and medical gases in cerebrovascular diseases. Med Gas Res. 2018;8(4):172-175.

Introduction

Cerebrovascular disease is one of the three major causes of death that poses a serious threat to human life. It has high morbidity, disability and mortality.[1] At present, the most mature cerebrovascular treatment is revascularization of acute cerebral infarction.[2] However, due to the narrow therapeutic time window of thrombolytic therapy and the complications of bleeding, it has great limitations for many stroke patients.[3] In this context, neuroprotective treatment has sprung up, and has achieve good results in basic research, becoming a new direction of stroke research. Neuroprotective treatment refers to the protection of brain parenchyma or brain cells, rather than revascularization, and can be used for the treatment of various cerebrovascular diseases.[4] Currently, there are several kinds of mechanisms involved in neuroprotective therapy, including ion channel modulators,[5] anti-excitotoxic drugs,[6] free radical scavengers,[7] neurotrophic factors,[8] hypothermia therapy (HT),[9] gene therapy and stem cell transplantation.[10] In addition, there are some gas researches on brain protection.[11] Among them, HT and medical gas therapy are increasingly concerned by researchers because of their convenience, speed and safety.

HT is currently a recognized and effective treatment.[12,13] Ischemic brain damage often occurs after cardiac arrest, and hypothermia is an effective treatment to prevent brain damage due to insufficient blood flow and improve brain function.[14,15] In 1987, Busto et al.[16] first proposed a systemic hypothermia (33–35°C) method for brain protection. The researchers defined a mild to moderate hypothermia at 28–35°C as a sub-hypothermia and found significant therapeutic and protective effects on experimental ischemia and experimental craniocerebral trauma in hypothermia range.[17] The mechanism of brain protection includes the following four aspects. Firstly, HT preserves the adenosine triphosphate required for metabolic recovery after cerebral ischemia by reducing energy expenditure[18]; secondly, it reduces the release of excitatory amino acids and reduce excitatory damage[19]; thirdly, it reduces the production of free radicals caused by ischemia[20]; fourthly, it prevents against ischemia-induced inhibition of calcium/calmodulin-dependent protein kinase II and protein kinase C.[21] This is a description about the therapeutic effect of hypothermia in the model of cerebral ischemia. In fact, hypothermia has anti-inflammatory and anti-apoptotic effects in all disease models.[22,23]

Medical gases are widely used in the medical field and provide solutions for a variety of medical needs. Medical gases such as oxygen, helium, xenon,[24] and hydrogen have been reported to have potential therapeutic effects and can treat a variety of brain diseases including hypoxia-ischemia, cerebral hemorrhages, and traumatic brain injuries.[25] Currently, xenon, which is a noble gas, has been reported to have neuroprotective effects.[26] Xenon may protect neurons by antagonizing N-methyl-D-aspartate receptors. Evidence reveals that xenon can provide protection and trophic support to neuron in a direct or indirect way.[27] Xenon originally reported to have brain protection in an ischemic model.

Experimental Studies

Hypoxic ischemic encephalopathy (HIE) presents an unnoticeable social burden with its high mortality and morbidity rates in the newborn population. HIE causes long-term neurological and behavioral impairment in the developing brain.[28] Induced therapeutic hypothermia has certified as an effective neuroprotective strategy for newborns with HIE.[29] However, about half of all treated neonates still die or face neurodevelopmental sequelae later in life.[30] Studies have shown that

vascular endothelial growth factor is expressed in the injured brain of neonates receiving hypothermia after an ischemic hypoxia event.[31] Studies have shown that when combined with hypothermia and inhaled xenon in treatment of ischemia and hypoxia, it has a synergistic effect and has a protective effect on the brain. Martin et al.[32] used 20% xenon combined with low temperature of 35°C to treat HIE in neonatal rats, which can significantly reduce the average brain area loss compared with single use. The researchers used a nylon thread to ligature the right common carotid artery for 1 hour, followed by ischemia and hypoxia for 90 minutes. After successful modeling, different interventions were found in groups, and no brain protection effect was found by using 20% xenon or 35°C low temperature treatment alone. When the two are used in combination, the volume of cerebral infraction can be significantly reduced. More interestingly, even if the two are not used synchronously, the cerebral infraction volume can be significantly reduced. Hobbs et al.[33] used standard neonatal hypoxic ischemic rat model. A total of 119 rat pups were randomized to juvenile control or experimental groups. Then, the experimental pups underwent left common carotid ligation under anesthesia. The rat pups that survived this hypoxic were randomly divided into four groups to recover for 3 hours at normothermia ($NT_{37°C}$) or hypothermia ($HT_{32°C}$) with or without 50% xenon ($Xe_{50\%}$) in the breathing gas. Afterwards, the rats were tested for early and late behavioral tests. Interestingly, hypothermia alone produced a functional improvement both short- and long-term testing, whereas $Xe_{50\%}$ shows only modest functional recovery in long-term behavioral test. Importantly, $Xe_{50\%}$ combined with $HT_{32°C}$ treatment showed the greatest improvement on both short- and long-term behavioral test. Similarly, the combination produced the greatest improvement in global histopathology scores, a pattern mirrored in the regional scores. So the $Xe_{50\%}$ $HT_{32°C}$ combination shows the greatest neuroprotection. Chakkarapani et al.[34] found that 24-hour HT provided 48% neuroprotection. Furthermore, combining 18-hour xenon with 24-hour HT offered 75% neuroprotection. The neuroprotective effects of HT-Xe were additive when administered together. It can significantly reduce histological injury. At the same time, they also found that a better extension of the hypothermia time can achieve better brain protection effects. However, when xenon combined with hypothermia for neonatal asphyxia, the clinical effect is not satisfactory.[35] The dose, timing, and duration of treatment with inhaled xenon might have been suboptimum. Therefore, clinical applications still require a large number of randomized controlled trails to verify.

Oxygen is the basis of all human activities, and is the driving force for the growth and development of life and life activities. From it has been discovered that oxygen can be used in treatment of several kinds of disease, it has been widely used in clinical practice. Importantly, the application of oxygen is no longer limited to a single disease.[36] Many studies have shown that the application of oxygen in cerebrovascular disease has become more and more mature.[37] For oxygen applications, the two current methods are normobaric hyperoxia (NBO) and hyperbaric oxygen. Hyperbaric oxygen can increase the partial pressure of oxygen, the diffusion rate of oxygen, and the effective dispersion distance. Directly improve energy metabolism in the ischemic or penumbra. After increasing the oxygen supply, hyperbaric oxygen has the function of contracting blood vessels, which can reduce total intracranial blood flow and reduce brain edema.[38] In addition, it also has anti-inflammatory, reduces the permeability of the blood-brain barrier, promotes thrombus absorption, and scavenges free radicals.[39,40] NBO is a treatment method in which a mask or an oxygen-absorbing hood is continuously inhaled in a normal pressure environment or a high-oxygen chamber is not pressurized, and a specific oxygen-absorbing device is used to absorb high-concentration oxygen. Studies have shown that there are similarities in the therapeutic mechanisms of NBO and hyperbaric oxygen. NBO can increase the blood oxygen partial pressure and blood oxygen content of the ischemic penumbra brain tissue to improve hypoxia.[41] In recent years, it has been found that hypothermia combined with oxygen therapy has a better effect on cerebrovascular diseases. Cai et al.[42] also found that NBO and hypothermia treatment can produce better brain protection. Sprague-Dawley rats were subjected to middle cerebral artery occlusion with an autologous embolus. In the experimental results, they found that NBO combined with HT exhibited an even greater reduction in neurological deficits. Furthermore, the combinations resulted in much greater reductions of infarct volume. Interestingly, relative to a single treatment, treatment with NBO + HT resulted in an larger drop in LDH levels at 24 hours.[42] Further studies have shown that a combination of NBO and HT can improve neuroprotection through ameliorating oxidative injury and improving pyruvate dehydrogenase regulation. Wada et al.[43] found that combination of hypothermia and hyperbaric oxygenation can reduce forebrain ischemia in the gerbil hippocampus. After the animals were anesthetized, they separated the common carotid artery of the gerbil, and then clamped the blood vessel with a blood vessel clamp, causing a transient hypoxia in the brain of the gerbil. After that, the gerbils are treated differently. Seven days after ischemic injury, the gerbils were sacrificed and their brains were removed for histological analysis. The results showed that although the hypothermia group and the hypothermia plus hyperbaric oxygenation group were able to reduce the pyramidal cells in the hippocampal CA1 region compared with the sham operation group, the hypothermia plus hyperbaric oxygenation group could significantly reduce the cell death.[43] This clearly demonstrates the combined effects of hypothermia and hyperbaric oxygen therapy (**Table 1**).

Clinical Studies

At present, the combination of hypothermia and medical gas has shown good application prospects in basic experiments, but the results of clinical studies are rare. Recent studies have found that when combined with hypothermia for treatment of neonatal asphyxia, the effect is not satisfactory, and side effects occur in the application of xenon. Azzopardi et al.[35] enrolled 92 infants, 46 of whom were randomly assigned to cooling only and 46 to xenon plus cooling. They performed a magnetic resonance assessment of the treated newborn. However, they noted no significant differences in lactate to N-acetyl aspartate ratio in the thalamus or fractional anisotropy in the posterior limb of the internal capsule between the two groups. The researchers speculated that the reason for the unsatisfactory clinical trial

Table 1: Studies regarding the combined use of hypothermia and medical gas for cerebrovascular disease

Reference	Year	Animal	Model	Results
Martin et al.[33]	2007	Sprague-Dawley rat	HIE	$Xe_{20\%}$ combined with low temperature of 35°C can significantly reduce the volume of cerebral infraction compared with single use.
Hobbs et al.[34]	2008	Rat	HIE	The $Xe_{50\%}$ $HT_{32°C}$ combination shows the greatest neuroprotection. $Xe_{50\%}$ combined with $HT_{32°C}$ treatment showed the greatest improvement on both short- and long-term behavioral test.
Chakkarapani et al.[35]	2009	Pig	HIE	The neuroprotective effects of HT-Xe were additive when administered. together. It can significantly reduce histological injury.
Cai et al.[43]	2016	Sprague-Dawley rat	MCAO	The combination of NBO and HT can reduce the damage level of neurological deficits and infract volume. In addition, it can be better reduced the level of LDH.
Wada et al.[44]	2006	Mongolian gerbils	BI	The hypothermia plus hyperbaric oxygenation group could significantly reduce the cell death in the hippocampal CA1 region.

Note: MCAO: Middle cerebral artery occlusion; HIE: hypoxic ischemic encephalopathy; BI: brain ischemic; Xe: xenon; HT: hypothermia therapy; NBO: normobaric hyperoxia; LDH: lactate dehydrogenase.

results may be due to the difference in the optimal time point and duration of the intervention method for the human body and the experimental animals. Researchers believed that the timing, dose, and duration of treatment with inhaled xenon might have been suboptimum. In addition, given the safety of clinical use, a large number of clinical randomized controlled trials are still needed to verify its effects. The current animal experimental protocol suggests that the combination of early hypothermia and delayed medical gas therapy is neuroprotection.[44] Furthermore, in clinical studies, the time points for the combination of hypothermia and medical gases, and duration of hypothermia and medical gases still require further experimental results to verify.

Conclusion

The combination of hypothermia and medical gas has shown great application prospects. The current studies mainly focused on the combination of hypothermia and xenon or oxygen, and have achieved gratifying results. However, there are still many aspects worth exploring such as the effectiveness of the combination of hypothermia and other medical gas. Further researches especially larger clinical trials are required to validate its effectiveness and guide its specific application.

Author contributions
Manuscript writing: HL; revision: XT; drafting and revision: QX and JHZ. All the authors read and approved the final version of the manuscript for publication.
Conflicts of interest
The authors have no conflict of interest.
Financial support
None.

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Received: 2018-08-28
Accepted: 2018-11-06