European Review for Medical and Pharmacological Sciences 2017; 21 (4 Suppl): 50-53

Hypothermia in neonatal hypoxic-ischemic encephalopathy (HIE)

G. LIU, Z.-G. LI, J.-S. GAO

Department of Neonatology, Xunzhou Children's Hospital, Xuzhou, Jiangsu, China

Abstract. – Neonatal hypoxic-ischemic encephalopathy (HIE) significantly affects neurodevelopment in infants and is also considered as an important cause of neonatal deaths worldwide. Medical research is being focused worldwide for the development of therapeutic avenues but it is still managed by supportive care. The latest studies in the above field have shown the efficacy of prolonged cooling of neonate's head or whole body at the age of 18 months (approx.) in providing relief from the pathological state of HIE. Moreover, hypothermia is the first reported therapeutic modality that proved beneficial for HIE young patients. Further, it acts by decreasing the cerebral metabolism to mitigate neurological outcomes of the pathological state. The present review article would discuss all-important aspects of hyperthermia therapy in the improvement of young patients affected by HIE.

Key Words:
Hyperthermia, HIE, Neonates.

Introduction

Hypothermia is associated with decline in cerebral metabolism and is the prime therapeutic intervention that can improvise neurological outcomes. The temperature has the ability to affect physiological metabolic rate of the physiological system. This idea forms the basis of moderate hypothermia therapy for the application as a neural rescue; however, it is still a dilemma[1]. To further understand in numbers, it was estimated that for every 10 degrees fall in the core temperature, cerebral metabolism declined to the tune of 7%, along with decline in glucose and oxygen demand[2]. Moreover, necrotic as well as apoptotic mechanisms were involved in neuronal injury following neonatal hypoxia-ischemia and reperfusion. On the whole, apoptosis was considered responsible for the progressive neuronal injury following neonatal hypoxia-ischemia. Moreover, a recent report noticed the reduction of free radicals, as well as glutamate levels following hypothermia therapy, which has provided another dimension of thought for mechanistic justification for the hypothermia therapy[3]. This act of reduction in free radicals and glutamate levels, in turn, helped in further protection of mitochondrial function and showed a decline in inflammatory responses. Another study noticed a significant decline in the caspase activity along with an increment of Bcl2 expression during hypothermia therapy[4,5]. Thus, inhibition of caspase and stimulation of Bcl2 emerged as one of the mechanistic effects of the hypothermia therapy. Figure 1 shows the underlying processes in pathophysiology and possible target points for treatment. The present review article would cover all the important aspects of hypothermia.

Proposed Mechanisms Behind Hypothermia Therapy

The exact mechanism responsible for neural rescue by application of moderate hypothermia is not certain. It might be related to the critical relationship between temperature and metabolic rate. Both necrotic and apoptotic mechanisms were implicated in neuronal injury following neonatal hypoxia-ischemia and reperfusion. The deprivation of oxygen and glucose caused by the reduction of cerebral blood flow leads to a severe decrease in high-energy phosphate reserves including adenosine triphosphate. The inability to maintain the polarity of the membrane, in neurons, as well as glial cells, results in energy failure of sodium-potassium-adenosine pump. So, this inability of sodium-potassium-adenosine pump finally causes excessive glutamate release within the synaptic cleft, leading to a significant influx of sodium as well as calcium to the cells. The elevation in calcium levels stimulates several enzymes including phospholipase, proteases, and endonucleases or nitric oxide synthase. The com-

Corresponding Author: Zhenguang Li, MD; e-mail: zhenguangli29@163.com

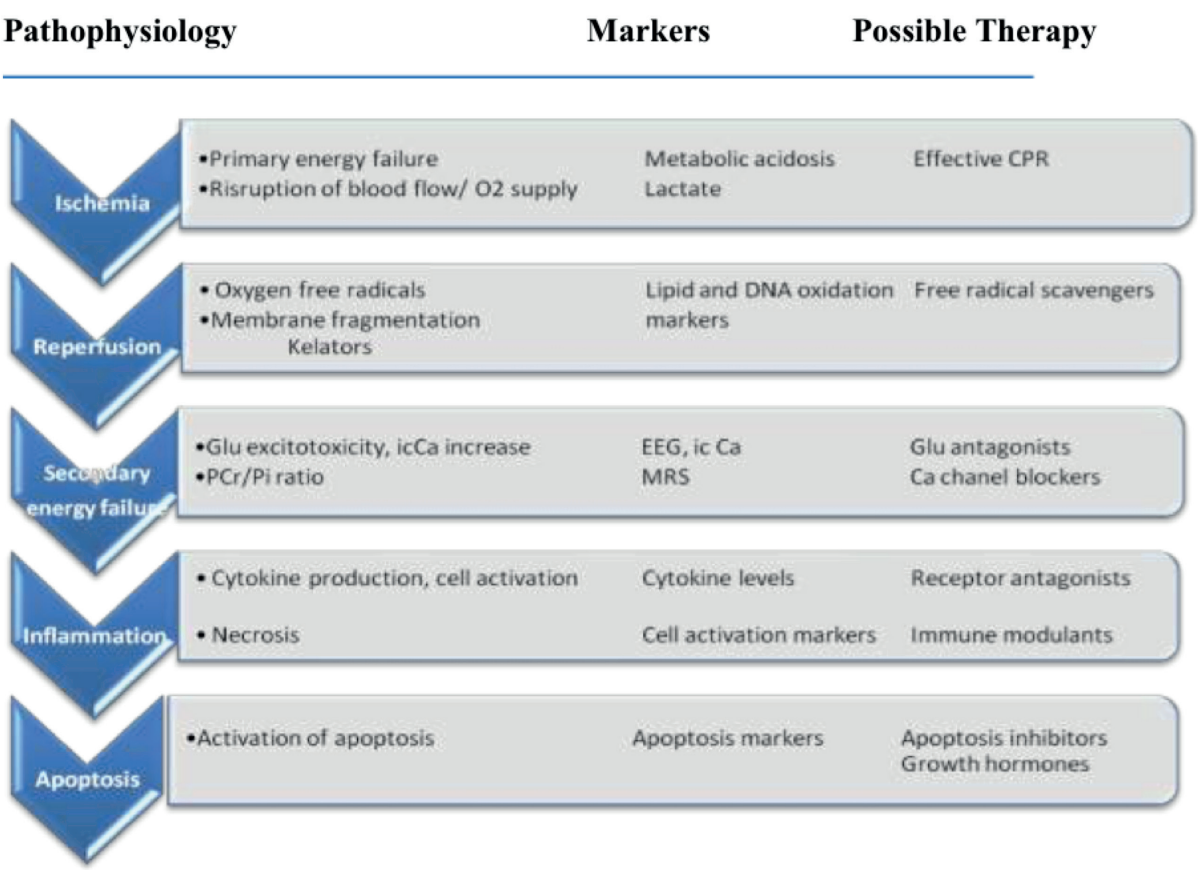

Figure 1. Various processes in pathophysiology and possible target points.

bined consequences of cellular energy failure, lactate acidosis, glutamate release, calcium accumulation and oxidative damage disrupt essential components of the cells that in turn cause death.

Clinical Evidence Supporting Therapeutic Hypothermia in Newborns

As discussed before, it is the prime therapeutic module for the hypoxic-ischemic encephalopathy patients and was initially thought to be the method of reanimation by immersion in cold water[6,7]. However, upon the development of experimental model of HIE and advancements in technological knowledge, later studies confirmed brief periods of post-insult, to be the main mechanisms working behind hypothermia[8,9]. The above mechanisms are documented as prime mechanisms responsible for observed neuro-protection in literature. Further, hypothermia therapy helps in significant healing during the trauma events like stroke, cardiac arrest or brain injury, as observed in earlier experimental human studies[9,10]. So, the above observations of the earlier studies confirmed the moderate hypothermia as an important therapeutic module during cerebral injury following hypoxic ischemia. Also, hypothermia resulted in the elevation of normal survival, thereby reduced rates of severe disability, cerebral palsy and improvised the developmental index. On the other hand, there are reports showing heterogeneity amongst the trials in severely encephalopathic infants undergoing hypothermia therapy. The only crucial complication observed to be associated with hypothermia therapy was the subcutaneous fat necrosis[11]. However, further researches, as well as experiences, are still required for reinsurance about the safety aspects of therapeutic hypothermia, especially in the cases of infants with systemic impediments like pulmonary hypertension or myocardial ischemia[12].

Some Uncertainties of Hypothermia

Despite observed remarkable results, there are some uncertainties in hypothermia therapy[13]. Firstly, no study has reported therapeutic hypothermia outcomes beyond 18 months of age in young infants. Secondly, despite the therapeutic efficacy of hypothermia therapy, 40% of infants

in the trials developed disabilities or showed mortality[14]. This might be the result of selection bias. Thirdly, there are limited or no studies on the application of therapeutic hypothermia in resource poor countries, where the incidence of hypoxic ischemic encephalopathy has greatly elevated. Further, a report from Uganda observed an increased mortality in the treatment group, which might be due to the chance allocation of infants with severe encephalopathy in the treatment group[15]. Therefore, field trials are essential extrapolation of hypothermia to variable environments in the near future.

Negative Aspects or Limitations of Hypothermia

One of the major problems in the pathway of the success of hypothermia therapy is its stressful procedure of inductance as well as maintenance. These conditions in turn, counteract the benefits of hypothermia therapy. Further, the supportive procedure adopted for the hypothermia therapy included maintenance of adequate sedation and analgesia during hypothermia. Moreover, in piglets, the neuroprotective effects of hypothermia were abolished in the absence of supportive adequate analgesia[16]. Therefore, it is considered highly important to have proper analgesia during hypothermia therapy. Furthermore, in infants when signs of distress and stress were visible during the total body hypothermia (TOBY), treatment with morphine was recommended for the proper ventilation[17]. Also, continuous assessment of the stress response is essential during hypothermia therapy, which is performed by observing signs of distress viz. tachycardia, irritability, facial grimacing and shivering. A heart rate consistently above 110-120 beats/min during hypothermia is another important indication for the immediate requirement of analgesia or sedation[17]. Hypothermia affects enzymatic processes, which in turn influence cellular functions of the physiological system of the patient under treatment[18,19]. To be more specific, a study showed reduction in the cerebral metabolism to the scale of 7% upon lowering of temperature by 1%[6]. Moreover, hypothermia affected the clearance of other therapeutic drugs in use[20]. However, there is paucity of information with regard to pharmacokinetics of drug in neonates undergoing hypothermia therapy. So, these are some of the important negative points to be worked on in the future for enhancing the applicability of this therapy in clinical setting as a standard gold technique.

Conclusions

The present review article highlighted both positive and negative aspects of hypothermia therapy during neonatal hypoxic-ischemic encephalopathy. The hypothermia therapy is an emerging therapeutic approach against hypoxic-ischemic encephalopathy, but some negative aspects have to be taken care of in the future.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) White CW, Ambrose E, Müller A, Li Y, Le H, Thliveris J, Arora RC, Lee TW, Dixon IM, Tian G, Nagendran J, Hryshko LV, Freed DH. Avoidance of profound hypothermia during initial reperfusion improves the functional recovery of hearts donated after circulatory death. Am J Transplant 2016; 16: 773-782.
2) Imataka G, Wake K, Yamanouchi H, Ono K, Arisaka O. Brain hypothermia therapy for status epilepticus in childhood. Eur Rev Med Pharmacol Sci 2014; 18: 1883-1888.
3) Thoresen M, Satas S, Puka-Sundvall M, Whitelaw A, Hallstrom A, Loberg EM, Ungerstedt U, Steen PA, Hagberg H. Post-hypoxic hypothermia reduces cerebrocortical release of NO and excitotoxins. Neuroreport 1997; 8: 3359-3362.
4) Fukuda H, Tomimatsu T, Watanabe N, Mu JW, Kohzuhi M, Endo M, Fujii E, Kanzaki T, Murata Z. Post-ischemic hypothermia blocks caspase-3 activation in the newborn rat brain after hypoxia-ischemia. Brain Res 2001; 910: 187-191.
5) Zhang H, Xu G, Zhang J, Murong S, Mei Y, Tong E. Mild hypothermia reduces ischemic neuron death via altering the expression of p53 and bcl-2. Neurol Res 2010; 32: 384-389.
6) Erecinska M, Thoresen M, Silver IA. Effects of hypothermia on energy metabolism in mammalian central nervous system. J Cereb Blood Flow Metab 2003; 23: 513-530.
7) Thoresen M, Penrice J, Lorek A, Cady EB, Wylezinska M, Krikbride V, Cooper CE, Brown GC, Edwards AD, Wyatt JS. Mild hypothermia after severe transient hypoxia-ischemia ameliorates delayed cerebral energy failure in the newborn piglet. Pediatr Res1995; 37: 667-670.
8) Bakhsheshi MF, Diop M, Morrison LB, St Lawrence K, Lee TY. Coupling of cerebral blood flow and oxygen consumption during hypothermia in newborn piglets as measured by time-resolved near-infrared spectroscopy: a pilot study. Neurophotonics 2015; 2: 035006.
9) Cattaneo G, Schumacher M, Maurer C, Wolfertz J, Jost T, Büchert M, Keuler A, Boos L, Shah MJ, Fo-

erster K, Niesen WD, Ihorst G, Urbach H, Meckel S. Endovascular cooling catheter for selective brain hypothermia: an animal feasibility study of cooling performance. AJNR Am J Neuroradiol 2016; 37: 885-891.

10) Kang IS, Fumiaki I, Pyun WB. Therapeutic hypothermia for cardioprotection in acute myocardial infarction.Yonsei Med J 2016; 5: 291-297.

11) Grass B, Weibel L, Hagmann C, Brotschi B; National Asphyxia and Cooling Register Group. Subcutaneous fat necrosis in neonates with hypoxic ischaemic encephalopathy registered in the Swiss National Asphyxia and Cooling Register. BMC Pediatr 2015; 15: 73.

12) O'Phelan KH, Merenda A, Denny KG, Zaila KE, Gonzalez C. Therapeutic temperature modulation is associated with pulmonary complications in patients with severe traumatic brain injury. World J Crit Care Med 2015; 4: 296-301.

13) Bel FV, Groenendaal F. Drugs for neuroprotection after birth asphyxia: pharmacologic adjuncts to hypothermia. Semin Perinatol 2016; 40: 152-159.

14) Rischall ML, Rowland-Fisher A. Evidence-based management of accidental hypothermia in the emergency department. Emerg Med Pract 2016; 18: 1-18.

15) Robertson NJ, Nakakeeto M, Hagmann C, Cowan FM, Acolet D, Iwata O, Allen E, Elbourne D, Costello A, Jacobs I. Therapeutic hypothermia for birth asphyxia in low-resource settings: a pilot randomised controlled trial. Lancet 2008; 372: 801-803.

16) Thoresen M, Satas S, Loberg EM, Whitelaw A, Acolet D, Lindgren C, Penrice J, Robertson N, Haug E, Steen PA. Twenty-four hours of mild hypothermia in unsedated newborn pigs starting after a severe global hypoxic-ischemic insult is not neuroprotective. Pediatr Res 2001; 50: 405-411.

17) Kozar M, Javorka K, Javorka M, Matasova K, Zibolen M. Changes of cardiovascular regulation during rewarming in newborns undergoing whole-body hypothermia. Neuro Endocrinol Lett 2015; 36: 434-438

18) Fritz HG, Holzmayr M, Walter B, Moeritz KU, Lupp A, Bauer R. The effect of mild hypothermia on plasma fentanyl concentration and biotransformation in juvenile pigs. Anesth Analg 2005; 100: 996-1002.

19) Iida Y, Nishi S, Asada A. Effect of mild therapeutic hypothermia on phenytoin pharmacokinetics. Ther Drug Monit 2001; 23: 192-197.

20) Michelsen LG, Holford NH, Lu W, Hoke JF, Hug CC, Bailey JM. The pharmacokinetics of remifentanil in patients undergoing coronary artery bypass grafting with cardiopulmonary bypass. Anesth Analg 2001; 93: 1100-1105.