

亚低温治疗对于HIE患儿生理的影响

周润泽, 韦红*

重庆医科大学附属儿童医院新生儿科, 国家儿童健康与疾病临床医学研究中心, 儿童发育疾病研究教育部重点实验室, 儿科学重庆市重点实验室, 重庆

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摘要

亚低温治疗作为改善新生儿缺氧缺血性脑病预后的治疗手段可能会对患儿的生理功能造成一定的影响, 由于缺氧缺血性脑病容易合并多器官功能衰竭因此更需要紧密检测亚低温治疗期间的各项指标。亚低温治疗会造成一过性血小板减少和窦性心动过缓, 其他机体影响并不明显, 甚至可能对于心肾功还有一定保护作用。其次还需警惕亚低温治疗过程中的药动学, 亚低温可能会延缓镇静剂的代谢过程。

关键词

缺氧缺血性脑病, 亚低温, 生理, 多器官功能衰竭

Effects of Subcooling Therapy on the Physiology of Children with HIE

Runze Zhou, Hong Wei*

Department of Neonatology, Children's Hospital of Chongqing Medical University, National Clinical Research Center for Child Health and Disorders, Ministry of Education Key Laboratory of Child Development and Disorders, Chongqing Key Laboratory of Pediatrics, Chongqing

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Abstract

Hypothermia as a therapeutic tool to improve the prognosis of neonatal hypoxic-ischemic encephalopathy may have a certain impact on the physiological function of the children, as hypoxic-ischemic encephalopathy is prone to combined multi-organ dysfunction syndrome, so it is more

*通讯作者。

important to closely monitor the indicators of the period of hypothermia treatment. Therapeutic hypothermia will cause transient thrombocytopenia and sinus bradycardia, other body effects are not obvious, and may even have a certain protective effect on cardiac and renal function. Secondly, we should also be alert to the pharmacokinetics of hypothermia; hypothermia may slow down the metabolism of sedatives.

Keywords

Hypoxic-Ischemic Encephalopathy, Therapeutic Hypothermia, Physiology, Multi-Organ Dysfunction Syndrome

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1. 引言

新生儿缺氧缺血性脑病(HIE)指围生期各种因素导致的脑组织部分或完全缺氧、脑血流减少或暂停引起的新生儿脑损害。HIE 仍是新生儿发病和死亡的重要原因之一[1]。亚低温治疗新生儿缺氧缺血性脑病(HIE)目前已被证能够显著改善预后,降低病死率以及脑瘫发生率,已成为 HIE 的常规治疗手段。然而 HIE 可引起多器官功能障碍(MOD),以牺牲非重要器官为代价来保证血液流向重要器官,从而导致多个非重要脏器出现功能障碍[2]。同时患儿的每一个生理过程都可能受到治疗性低温的影响。本文旨在探讨在亚低温治疗对机体功能的影响。

2. 心血管

围产期窒息本身会导致心功能降低[3],而亚低温治疗本身会进一步降低心脏功能[4]。研究表明,降温时左心室心输出量是降温后水平的 67%,主要是由于心率降低,但也受搏出量减少的影响[5]。与收缩力关系最密切的心脏指数是收缩期峰值变异率[6],与健康组对比,HIE 患儿在最初 24 小时内的收缩期峰值变异率较低,这表明亚低温确实对心脏收缩力有影响。然而复温后,亚低温治疗患儿的数值可恢复正常,而未降温婴儿的数值则没有。与健康对照组或复温后的婴儿相比,未接受亚低温治疗患儿变异率明显更低[4]。因此降温可能对心肌有一定的保护作用。心动过缓是开始降温后最常见、最明显的心血管变化,心率低于 80 次/分钟,在临床上良性的[7]。心率过低可能是由于降温导致细胞内钙释放减少,从而减缓了窦房结复极化[8]。在推荐的亚低温治疗温度下发生心律失常是罕见的,同样目前没有证据表明亚低温治疗与低血压之间有明显关系[7]。

为了保证重要器官的供血,缺氧会引发儿茶酚胺分泌的增加,从而使外周血管收缩,同时持续的缺氧还会导致肺血管阻力增加和肺动脉高压[9]。动物模型显示肺血管阻力增加其程度随温度变化而变化,温度越低平均动脉压越高[10]。虽然有研究显示在亚低温期间需要吸入一氧化氮治疗肺动脉高压风险较高或一些患儿需要的氧浓度升高[11][12],并且有超声心电图提示亚低温期间肺血管阻力增加,然而复温后是可逆的[13]。出现肺动脉高压的风险无论是呼吸衰竭还是心输出量低下都取决于低温治疗前的心血管状态,并且是因人而异的。其更多与围产期窒息的潜在因素或者是对持续的生后低氧血症的反应有关,而非亚低温治疗。肺动脉高压的风险与需要一氧化氮治疗在亚低温与非亚低温治疗患儿之间并没有差异[7][14]。

3. 血液与肝脏

亚低温可能会影响血液学参数,特别是凝血功能,可能导致患儿出血风险增加或因为微循环减少可能会增加微栓塞和弥散性凝血病的风险[15]。低温可能也会影响白细胞功能,然而,对于目前推荐的亚低温治疗控制的温度范围,并不会导致脓毒症的风险增加[14]。对于目前推荐的亚低温治疗方案似乎也并不会恶化凝血或肝功能异常。研究显示冰帽降温治疗,有38%患儿存在肝功能受损以及约19%的患儿有凝血功能障碍[16],然而亚低温治疗与严重的凝血障碍引起的出血或严重血栓形成的发生率以及对于肝功能障碍均没有显著统计学意义[7]。

目前已证实亚低温治疗与一过性血细胞减少有关[7],不过与亚低温相关的血小板减少并不会导致出血增加[17]。虽然亚低温本身并不会导致凝血或肝功能障碍,但在亚低温治疗中仍需密切监测凝血、肝功能,因为需要干预的凝血障碍在HIE患儿中占有第二常见的发病率[18]。

4. 肾功能、电解质及血糖

一项纳入96名进行亚低温的窒息患儿的试验中,有36名(38%)发生了急性肾损伤(AKI),表明在接受亚低温治疗的患儿中AKI发生率仍然很高,但是低于亚低温出现之前的比率,证实亚低温治疗可能对肾功能有一定保护作用[19]。在亚低温治疗过程中肾小球血流通常不受影响,一篇纳入了6项研究(667名患儿,RR 0.8,95% CI 0.7~1.0)的荟萃分析中,亚低温治疗患儿的急性肾损伤发生率与常温治疗患儿无差异[7]。

然而AKI继发的电解质紊乱可能影响亚低温治疗期间的稳态。超过一半的患儿在亚低温治疗中出现电解质异常,其中低钠血症、低钾血症和低钙血症最为常见[20]。降温出现低钾血症,可能与纠正酸中毒后钾离子向细胞内转移有关,然而是否采用亚低温治疗的患儿之间相比低钾血症、低钙血症发生率并无统计学显著差异性[7][21],但需要警惕出生后不久若血钙浓度较低,可能提示HIE患儿预后较差[22]以及在对症纠正低钾血症后复温过程中可能出现高钾血症。

亚低温会刺激胰高血糖素分泌并降低胰岛素释放和胰岛素敏感性[23]。不过由于血糖受多种因素影响,如应激、炎症以及治疗过程中应用激素、营养支持等情况,因此亚低温对于血糖的影响难以说明[24]。

5. 胃肠道

由于窒息或缺血时会优先保证大脑、心脏和肾上腺的血供[25],新生儿可能会出现胃肠道缺血,从而导致坏死性小肠结肠炎或肠穿孔,但是这些发生率都极低,并且无论是否进行亚低温治疗,坏死性小肠结肠炎的发生率都相似[15]。在一项非随机对照研究中显示,亚低温治疗早期开始微量肠内营养也并不会增加NEC发生率[26]。

6. 药物代谢

通常窒息患儿用到的药物有抗生素、抗惊厥药物、镇静剂、血管活性药物等,药物的转化通常经过肝脏中细胞色素酶代谢,代谢是大部分药物从体内消除的主要方式。另外肾脏是药物排泄的主要途径。亚低温治疗可能会改变代谢和排泄进程[27]。研究发现亚低温治疗期间常用的抗惊厥药或镇静剂(如苯巴比妥、咪达唑仑等)、包括皮质类固醇等这些药物的代谢减慢[28][29],血浆浓度更高,半衰期比常温治疗的新生儿更长。因此在治疗HIE所致的癫痫期间应严密检测血药浓度。另外也有研究显示对于常用的针对败血症的庆大霉素亚低温并不会影响其血清水平[30]。由于其主要通过肾脏排泄,因此对于肾功能不全患儿应进行剂量调整。血管活性药物目前在常温和亚低温治疗患儿使用需要方面并没有显著差异性[20]。

当然在亚低温复温过程中也可能引起药动学改变。复温过程中分布在外周组织中的药物可能加速进入循环过程, 是患儿暴露于更高的血药浓度中。对于亚低温期间半衰期延长的药物, 复温期间可能会更快地清除从而导致疗效降低[27] [31]。

7. 结论

亚低温治疗 HIE 已成为常规治疗手段。亚低温可能对患儿的每一个生理过程都产生影响。血小板减少和窦性心动过缓是亚低温最常见的不良反应, 除此之外并不会对 MODS 的发生率以及程度产生有意义的影响。

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