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亚低温治疗在创伤性脑损伤中的应用进展

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摘　要

创伤性脑损伤(Traumatic Brain Injury, TBI)因其高发病率、高重症化率以及高致残率给社会带来沉重经济负担，因此改进其治疗手段一直是临床研究重点与热点。亚低温治疗(Hypothermic Therapy, HT)目前已经广泛应用于临床许多疾病的治疗；但HT在TBI的治疗中仍旧面临许多问题亟待解决。本文我们从Pubmed、Web of science、知网等平台根据关键词“创伤性脑损伤”、“亚低温治疗”、“创伤性脑损伤 + 亚低温治疗”搜索近5年文献，在去掉重复性文章、病例报告、初步报告(未经证实数据)等文献后筛选出274篇文献作为备选。然后我们邀请重庆市内具有临床教学资质的三级甲等综合医院重症医学科、神经学科主任医师各2名，这4名专家综合讨论评估后最终筛选出59篇文献。本文就HT在TBI治疗中的诸多问题做一综述，进一步明确其实际价值以及未来的研究方向。

关键词

创伤性脑损伤，亚低温治疗

Advances in the Application of Hypothermia Therapy in Traumatic Brain Injury

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Abstract

Traumatic Brain Injury (TBI) imposes a heavy economic burden on society due to its high incidence, high severity rate, and high disability rate. Therefore, improving its treatment methods has long

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been a key focus and research hotspot in clinical medicine. Hypothermic Therapy (HT) is currently widely used in the treatment of many clinical conditions; however, HT still faces numerous challenges in the management of TBI that require urgent resolution. In this study, we searched the literature from the past 5 years on platforms including PubMed, Web of Science, and CNKI using the keywords "Taumatic Brain Injury", "Mild Hypothermia Therapy", and "Traumatic Brain Injury + Mild Hypothermia Therapy". After excluding duplicate articles, case reports, preliminary reports (with unconfirmed data), and other irrelevant literature, 274 articles were selected as candidates. We then invited 2 chief physicians from the Department of Critical Care Medicine and 2 chief physicians from the Department of Neurology, all from tertiary Class A general hospitals with clinical teaching qualifications in Chongqing, resulting in a total of 4 experts. Following comprehensive discussion and evaluation by these experts, 59 articles were ultimately included. This paper reviews several issues regarding HT in the treatment of TBI, to further clarify its practical value and future research directions.

Keywords

Traumatic Brain Injury (TBI), Hypothermic Therapy (HT)

1. 引言

作为神经外科最常见的急性颅脑损伤类型，创伤性脑损伤(Traumatic Brain Injury, TBI)指的是外界机械外力直接或间接作用于头部，引起脑组织发生器质性损伤或功能性神经功能、认知、情感等方面障碍的一组急性创伤综合征；其可单独发生、也可能合并颅骨、肢体、脊柱等其他部位损伤；TBI 有别于脑卒中、脑血管意外等其他非创伤性颅脑损伤疾病。其严重程度目前主要由格拉斯哥昏迷量表(Glasgow Coma Scale, GCS)进行判定，即轻度(13~15)、中度(9~12)以及重度(3~8, Severe Traumatic Brain Injury, STBI)。

尽管亚低温治疗(Hypothermic Therapy, HT)最早可以追溯到希波克拉底时期；但实际上直到上个世纪其临床应用才有所进展。同时这一时期的大量临床实验至今仍充满争议——不管是坦普尔费伊的“人体冷藏实验”还是达濠的“低温实验”[1] [2]。通过人工主动干预的方式将机体核心体温精准降低到32℃~35℃的低温状态并维持一段时间后缓慢复温以此减轻中枢神经系统继发性损伤、保护神经细胞功能的一种靶向治疗手段即被称为 HT；该技术是神经系统等重症领域重要的颅脑保护策略，也是 TBI、心脏骤停后脑缺血缺氧、大型外科手术等疾病的核心治疗措施之一[3]。尽管该技术目前已经广泛应用于临床，但仍有许多问题存在争议，例如目标温度的设置、亚低温持续时间、降温手段选择以及复温过程等。研究证实啮齿动物大脑的冷却与复温较人类大脑更快实现并且控制能力更强，这是由于热质量的巨大差异所导致。这就意味着低温的关键参数很难从实验室转化到临床实际应用。

2. 亚低温深度

亚低温使得脑血流量显著减少，严重时诱发心律失常等并发症导致其最终结局是利大于弊。同时目前研究数据表明当下大多临床前实验目标温度为 33℃~34℃，而临床试验目标温度多在 33℃~35℃。但目前尚无数据支持更低温度(32℃) [4]时患者是否仍旧能获益。同时如何在低温对神经系统保护作用与低温引起颅内灌注不足之间权衡利弊，也是无法回避的问题之一[5]-[7]。最新实验证实 34℃~35℃其获益明显高于损伤；但美中不足的是样本量偏少，这就意味着需要更多数据支持[8]。

目前尚无针对诱导和监测脑温度的统一标准。许多临床研究并未直接测量脑温度而是通过其他部位温度进行估测，例如直肠温度或者膀胱温度。研究表明大鼠实验中其直肠温度为30℃时对应脑温度可能高达33℃ [9]。这就意味着如果预设定脑温度为33℃~35℃时，其实际温度可能超过35℃——之所以这么认为是因为类似于大鼠的温度梯度在人类同样适用；而这一实际温度很有可能无法对神经系统起到保护作用[10] [11]。更严重的时，直肠温度由于其时间滞后性、患者隐私暴露以及操作不便等问题，使得其实用性进一步下降[12]。因此如何更准确监测脑温度，成了当下重点探究的热点之一。部分研究证实鼓膜温度可能更准确[13]。另外，术前磁共振成像(Magnetic Resonance Imaging, MRI)光谱已经被用于脑温度的监测与颈动脉内膜切除术后颅内灌注的监测。但MRI与CT谁更能成为其首选诊断工具，需要更远的路要走。同时人工智能与数学建模的异军突起，也将在这一领域扮演重要角色[14]。

另一项对比了HT不同时间(48 h与120 h)的研究发现当亚低温时间超过48 h时，轻度低温(35℃~36℃)有利于结果改善[15]。性别对体温控制影响的报道尚需更多数据，尽管部分研究认为女性在出院时情况更好[16]；但30天生存率以及180天时的神经系统功能恢复则没有明显差异[17]。

3. 低体温持续多久？

目前临床实际低温持续时间通常超过12 h，但动物实验则多维持在1 h~3 h [18]。由于TBI持续时间很长，治疗周期长，因此更长时间维持低温可能获益更多。但长期低温治疗会增加各种不良反应的风险，包括内环境紊乱、感染、免疫抑制以及院内感染[19]-[21]。一项多中心实验指出低温治疗超过12 h后患者发生肺部感染风险超过50% [22]。在大鼠TBI模型中，通过将6 mL 20℃生理盐水灌注到动脉内，可使得大脑皮层与纹状体温度迅速下降至33.4℃与33.9℃并维持1 h [23] [24]。这就意味着短时间的局部低体温治疗时具有临床可行性的，尤其是针对TBI的再灌注治疗。

另外受当下技术限制、从开始降温到达到预期设定温度通常需要不少于4 h；这就模糊了HT的具体时间－到底是从体温下降初期即开始计算时间还是只计算目标体温持续时间。部分学者称之为“有效低温持续时间”。即大脑温度在35℃以下直至重新恢复到正常温度的时间段，而不是HT总持续时间[25]。同时他们坚持认为将这一时间设定为2 h~4 h为最佳有效时间。

4. 复温速度

复温过程较之降温过程同样重要；动物实验揭示复温过快导能导致神经系统损伤、破坏血脑屏障(Blood-Brain Barrier, BBB)甚至诱发炎症[26]。另一研究发现复温过快可能导致颅内压骤变、高钾血症以及随之诱发恶性心律失常[27] [28]。目前认可的标准复温方案认为整个过程不应少于12 h；以患者为中心的个体化复温方案逐渐被倡导，尤其是对于重症患者[29]。对于发热高危人群，自然复温可能减少体温骤升的可能性以及高热对机体的损伤[30]。但整体而言，对复温过程的研究更少，这就意味着需要更多的研究来指导如何更科学的复温。

5. 临床延迟

尽管动物实验可以在TBI发生后1 h内进行HT；但这并不意味着临床实际应用中也能做到如此快速反应。从发现患病到明确诊断这一过程具体需要多久时间目前尚无大规模数据进行判定，但通常认为这一时间远远超过1 h [31]。从院前转运、院内诊断到医患沟通确定治疗方案，均需要消耗时间，而这些步骤很可能导致错过最佳治疗时间[32]。因此，临床实践中很难做到发病后立即接受HT。研究表明TBI后尽早开展HT并辅助以其他治疗手段可能最有利于患者最后结局。这也就意味着院前HT可能会成为一个具有前景的治疗手段[33]。这并不是幻想，随着可移动CT和TBI移动单元的部署、训练有素急救人员的配备以及便携式冷却头盔等新型设备的出现，在未来HT完全可以在救护车里进行[34]。

6. 临床前研究与临床应用的差异

动物模型的成功和普及并不意味着人体实验同样成功，这是因为不管是降温速度、复温速度还是其他方面，体型更小的动物较之人体均具有显著差异。例如在动物模型中行之有效的冰毯或局部冰敷以及冰头盔在临床试验中并未达到理想的神经系统保护作用[35] [36]。更新冷却设备有助于解决上述问题，尤其是局部降温技术的研发，这不仅能提高冷却效率，还能减少对核心体温的降低，减轻对其他重要器官的损伤[37]。但其时效性与可行性则需要进一步验证[38]。

7. 降温手段的选择：从全身性冷却到局部冷却

包括酒精浴、冰毯以及对流空气毯在内的体表冷却手段由于操作简单而一直是诱导亚低温的基石；但同时其低效率，可能诱发寒战、凝血功能障碍、感染等副作用严重限制其实际应用[39]。冷却头盔等局部冷却手段的出现有效解决上述问题；尤其是其便携性使得院前 HT 成为了可能。采用鼻内球囊导管加注循环生理盐水是另外一种局部脑冷却手段；但其可操作性及时效性则需要更多数据支撑[40]。尽管鼻内球囊提高了冷却效率，但它们仍然不能在合理的时间范围内达到目标温度[41]。因此，也有人提出开发更复杂的设备，可以快速安全地冷却大脑[42]。例如 Li 等人巧妙地设计并构建一种用于导尿管的硅基中空微颗粒结合丝素隔热涂层，与无涂层的导管相比，其显示出优越的冷却效率并已经成功用于猪模型动物实验[43]。

其他治疗手段例如早期持续预防性低温治疗(Early Sustained Prophylactic Hypothermia, ESPH)、Eurotherm 3235 对神经系统功能的长期预后目前仍需要更多数据支持，其他次要结局包括死亡率、预先定义的亚组、方案分析或治疗分析等也缺乏更多的益处[44] [45]。其他方面如对颅内压的改变也需要更多研究进一步证实[46]。

8. 药物降温

如果说物理降温旨在降低体温，那么药物降温则不仅能达成这一目的，还能起到治疗作用[47]。异丙嗪和氯丙嗪的经典组合已经明确证实其具有神经保护功能并广泛应用于临床。因此，一旦确定了治疗窗口与治疗剂量，药物冷却可快速缓解症状，加速冷却过程，延长持续的冷却时间并增强神经修复与再灌注效果[48]。目前已经证实二氢辣椒素可预防远端继发性损伤并有助于 TBI 后器官功能恢复[49]。神经紧张素受体激动剂 HPI-201 可显著减轻炎症爆发的风险并能保护神经元功能[50]。其他药物诸如神经紧张素、甲状腺素等也逐渐被证实具有药理冷却及对抗寒战功能[51]。但需要警惕的是这些药物可能对机体带来其他损伤，因此需要严格判定药物使用的收益与风险。

9. 从单一冷却方法到多种冷却方法的组合

动物实验表明物理降温与药物降温联合不仅能更快速降低体温，还能降低不良反应发生的风险；但临床实际应用则需要更多数据支持[52]。另外一个新的思路是通过体外回路将冷却的自体血液直接注入大脑，这一思路似乎有效解决大脑冷却所需液体量的难题；动物实验已经证实其不仅能有效诱导局部快速降温，还能保持大脑白质的完整性并有利于功能恢复。这就意味着自体冷却血液输注可能用于临床转化[53] [54]。另外需要关注的是一些药物的增强 HT 效果已经被证实。例如重组高密度脂蛋白在抗炎与抗氧化特性以及 BBB 通透性方面已经显示出显著优势；这就意味着其在抗炎抗氧化同时还能有效改善神经元功能、减轻神经系统损伤[55] [56]。

10. 并发症

在思考 HT 给患者的获益时，也不能不考虑其可能存在的风险或各种并发症。首先需要警惕的是低

体温给患者带来的直接损伤，低温抑制多核细胞中热休克蛋白 60 表达，该细胞通过激活树突状细胞与其他细胞诱导免疫激活；因此低温可能会抑制免疫系统进而增加感染风险[57]。但也有研究认为低体温不会增加炎症反应或感染的风险[58]。HT 是否增加再发脑出血风险目前尚无定论，因为部分研究支持其风险增加但也有研究认为没有影响[44] [59]。

11. 总结

上述数据表明 HT 在 TBI 中的应用仍处于比较初步的状态；尤其是实验室与临床实际应用的脱节。大规模多中心的随机实验对照是十分必要的，包括目标低体温选择、目标低体温持续时间、复温速度、局部或全身性 HT 以及降温手段的选择等多方面；HT 时机的选择，尤其是如何在院前尽早 HT 或治疗前准备目前尚未取得突破性进展，这涉及院前急救水平的重大提升与改革；HT 给患者带来的利弊评判等伦理考量也必须被重视，因为医疗的初衷永远都是把患者利益放在首位。

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