

极/超早产儿早期使用氢化可的松的研究进展

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收稿日期: 2025年12月7日; 录用日期: 2026年1月1日; 发布日期: 2026年1月9日

摘 要

极/超早产儿生后由于下丘脑-垂体-肾上腺轴功能发育不成熟, 易发生短暂肾上腺皮质功能不全。氢化可的松具有抗炎、改善血管通透性及稳定血流动力学等作用, 临床上早期应用于低血压防治、预防支气管肺发育不良等, 但其使用所带来的不良反应也限制了其应用, 目前氢化可的松使用的获益风险比仍尚未明确。本文综述了氢化可的松的药理作用、药代动力学、临床应用现状及相关不良反应, 以期极/超早产儿早期使用氢化可的松提供循证证据和临床策略。

关键词

早产儿, 氢化可的松, 有效性, 安全性

Research Advances in the Early Use of Hydrocortisone for Extremely/Very Preterm Infants

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Received: December 7, 2025; accepted: January 1, 2026; published: January 9, 2026

Abstract

Due to immaturity of the hypothalamic-pituitary-adrenal axis, very preterm and extremely preterm

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文章引用: 胡微, 史源. 极/超早产儿早期使用氢化可的松的研究进展[J]. 临床医学进展, 2026, 16(1): 803-810.
DOI: 10.12677/acm.2026.161107

infants are at risk of transient adrenal insufficiency. Hydrocortisone, with its anti-inflammatory properties, ability to improve vascular permeability, and hemodynamic-stabilizing effects, is clinically utilized for the early management of hypotension and for the prevention of bronchopulmonary dysplasia in this population. However, the associated adverse effects constrain its broader application, and the overall benefit-risk balance of hydrocortisone remains uncertain. This review comprehensively examines the pharmacological characteristics, pharmacokinetics, current clinical uses, and relevant adverse effects of hydrocortisone, aiming to provide evidence-based insights and practical strategies to guide its judicious early administration in very and extremely preterm infants.

Keywords

Preterm Infant, Hydrocortisone, Efficacy, Safety

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1. 引言

随着围产医学与新生儿重症救治技术的显著进步,胎龄小于32周或出生体重小于1500克的极/超早产儿的存活率正逐步提升[1][2]。然而,存活率提高的同时也使此类患儿的特殊生理问题愈发凸显,由于其下丘脑-垂体-肾上腺(hypothalamic-pituitary-adrenal, HPA)轴功能发育不成熟,发生短暂性肾上腺皮质功能不全(transient adreno-cortical insufficiency of prematurity, TAP)现象的风险极高[3],TAP不仅可能引发循环功能衰竭、内环境紊乱等急性并发症,更与支气管肺发育不良(bronchopulmonary dysplasia, BPD)、早产儿视网膜病变(Retinopathy of prematurity, ROP)及神经功能损伤等严重并发症密切相关[4][5]。临床数据显示,TAP多见于胎龄<30周的早产儿,通常发生于生后早期,持续时间较少超过生后14天[3][6]。针对这一关键临床问题,近年来多项研究表明,生后一周内对极/超早产儿预防性或治疗性使用氢化可的松,可降低出院前死亡率、提高无BPD存活率、促进动脉导管闭合,并对稳定血流动力学、调节糖代谢、辅助ROP治疗产生积极影响[7]-[11]。基于此,本文旨在综述极/超早产儿早期应用氢化可的松的有效性及安全性。

2. 氢化可的松的药理作用

近年来对氢化可的松的药理机制研究日益深入,其作用途径已被多维度阐明,核心在于通过调控生理通路实现对多系统的保护与调节效应。在循环系统中,氢化可的松的作用呈现多靶点特征:一方面通过增加心血管肾上腺素能受体密度、上调心肌血管紧张素受体基因表达、逆转儿茶酚胺长期暴露所致的受体脱敏,以及抑制一氧化氮合成等途径增加心血管调节能力[12][13];另一方面通过改善毛细血管通透性、增加细胞内钙等方式[14],强化心血管系统对外源性及内源性血管活性物质的反应性,最终实现升血压、稳定血流动力学的关键作用;此外,其抗炎作用可以抑制花生四烯酸释放和前列腺素合成,这一机制也为促进动脉导管闭合提供了重要支撑[15]。在呼吸系统方面,氢化可的松的核心作用围绕炎症调控展开,通过靶向核因子- κ B (NF- κ B)与环氧化酶-2 (COX-2)信号通路[7],发挥抗炎、免疫调节、稳定细胞膜及调控细胞因子分泌等多重作用,进而减轻肺部炎症损伤,改善呼吸功能[16][17]。在代谢方面,氢化可的松通过减少糖原合成、促进糖异生并降低外周组织对葡萄糖的摄取和利用,从而参与血糖调控,维持血糖稳态[18][19]。此外,氢化可的松还具有稳定血脑屏障结构、降低白质损伤风险、以及抑制氧化应激

与细胞凋亡通路等作用, 对神经系统发育产生积极影响, 为早产儿神经发育提供保护[20]。

氢化可的松的药代动力学特征在新生儿中呈现显著的发育依赖性, 这一特点影响临床用药策略。该药物半衰期短, 组织分布广泛, 药代动力学过程受胎龄、肝肾功能成熟度及临床疾病状态的影响, 相较于地塞米松等长效糖皮质激素, 氢化可的松在新生儿体内的清除率较高, 主要经肝脏代谢后通过肾脏排泄[20]。但早产儿肝肾功能尚未发育成熟, 药物代谢与排泄能力受限, 导致药物暴露量存在较大的个体差异, 尤其在极低出生体重儿中易出现蓄积风险, 导致游离药物浓度升高, 这一现象在增强药理效应的同时也增加了不良反应的发生率[21]。因此, 临床应用中需依据患儿体重、胎龄及治疗效果动态调整剂量, 实施个体化给药方案, 并密切监测血糖、电解质及血压等核心代谢及循环指标, 以实现疗效与安全性的平衡。

3. 氢化可的松在极/超早产儿中的应用

3.1. 预防性应用

3.1.1. 低血压的预防

新生儿低血压定义为平均动脉压低于同胎龄新生儿平均动脉压的第 10 百分位数(适用于胎龄 < 30 周、生后 3 天内的早产儿)[22], 是极/超早产儿群体中常见且严重的并发症, 其发生与脑室内出血、脑室周围白质软化及影响神经系统发育等不良结局相关[6]。多项研究表明, 生后预防性使用氢化可的松有助于稳定循环功能并降低后续血管活性药物的使用需求。Efird 等的研究表明, 生后使用氢化可的松(1 mg/kg q12h*2 天, 0.3 mg/kg q12h*3 天, 总剂量 5.8 mg/kg)可以减少对其他血管加压药的使用需求[23]; Watterberg 等的试验进一步指出, 预防性使用氢化可的松(0.5 mg/kg q12h*12 天, 0.5 mg/kg qd*3 天, 总剂量 13.5 mg/kg)能有效提升患儿的平均动脉压[24]; Baud 等的研究也支持该结论, 其采用的方案(0.5 mg/kg q12h*7 天, 0.5 mg/kg qd*3 天, 总剂量 8.5 mg/kg)显著减少了多巴胺类药物的使用[25]。

3.1.2. BPD 的预防

BPD 是极/超早产儿常见的慢性肺部疾病, 发生率达 8%~35%, 可导致远期肺功能损伤和严重的长期神经发育障碍[26], 多项研究已经论证了氢化可的松预防 BPD 的有效性。Watterberg 与 Bonsante 等的两项研究结果均表明, 生后使用氢化可的松(1 mg/kg*9 天, 0.5 mg/kg*3 天, 总剂量 10.5 mg/kg)提高了患儿无 BPD 生存的可能性[27][28]; 虽然 Watterberg 等的研究未明确得出使用氢化可的松(1 mg/kg*12 天, 0.5 mg/kg*3 天, 总剂量 13.5 mg/kg)能提升整体无 BPD 的生存率, 但发现对暴露于绒毛膜羊膜炎的婴儿使用该方案可显著降低死亡率并提高无 BPD 的生存率[24]; Peltoniemi 等则观察到, 早期使用氢化可的松(2 mg/kg*2 天, 1.5 mg/kg*2 天, 0.75 mg/kg*6 天, 总剂量 11.5 mg/kg)可提升皮质醇水平偏低患儿无 BPD 生存率[29]; 此外, Hochwald 等的研究显示, 采用氢化可的松治疗(首剂 2 mg/kg, 1 mg/kg q6h*3 剂, 0.5 mg/kg q6h*4 剂, 总剂量 7 mg/kg)可降低 BPD 发生率[30]; Shah、Baud、Briscoe、Petrishka-Lozenska 等多人多项研究也共同支持, 生后预防性使用氢化可的松(0.5 mg/kg q12h*7 天, 0.5 mg/kg qd*3 天, 总剂量 8.5 mg/kg)有助于提高无 BPD 生存率[9][25][31][32]。尽管现有研究尚未明确氢化可的松用于预防 BPD 的确切剂量, 但临床共识已逐渐倾向于采用低剂量(1~2 mg/kg/d)及低总剂量方案, 在保证疗效的同时降低不良反应风险。

3.1.3. 预防性用药的其他潜在影响

除低血压与 BPD 外, 氢化可的松在极/超早产儿其他并发症的管理中也展现出潜在价值。在动脉导管未闭防治方面, Baud 等的研究发现预防性使用氢化可的松可降低动脉导管未闭的手术结扎率[25]; Shaffer 等的 Meta 分析也指出, 预防性用药能减少早产儿出院前死亡率以及动脉导管未闭的治疗率[33]。在新生

儿坏死性小肠结肠炎防治领域, De Luca 等的荟萃分析发现氢化可的松的使用与该病发生率下降相关[34], 这一效果可能与其维持血压、促进动脉导管闭合, 进而增加肠系膜血管灌注有关, 但该机制仍需大型对照试验验证。此外, Petrishka-Lozenska 等的回顾性研究提示, 用于预防 BPD 的产后早期低剂量氢化可的松的使用可能降低极早产儿 ROP 的治疗风险[32], 然而这一结论同样有待更高质量研究进一步证实。

3.2. 治疗性应用

对于已出现低血压甚至休克的早产儿, 氢化可的松在难治性病例中的治疗作用已受到关注, 既往文献报道, 大约 26%到 48%的低血压新生儿对常规容量复苏、血管升压药物及正性肌力药物治疗效果不明显, 而对皮质类固醇治疗敏感[35]。Pak C Ng 等开展的一项双盲随机对照研究证实, 采用应激剂量氢化可的松(1 mg/kg q8h*5 天, 总剂量 15 mg/kg)可有效改善顽固性低血压[36]; Hochwald 等的研究进一步显示, 与安慰剂相比, 氢化可的松治疗组(首剂 2 mg/kg, 1 mg/kg q6h*3 剂, 0.5 mg/kg q6h*4 剂, 总剂量 7 mg/kg)的平均动脉压显著升高, 且多巴胺的使用剂量与时间均更短[30]; 然而 Dudeja 等的研究则指出, 当氢化可的松治疗组(1 mg/kg q6h*2 天, 1 mg/kg q12h*3 天, 总剂量 18 mg/kg)与安慰剂组同时在接受血管活性药物治疗时, 两组间主要结局未显示出统计学差异, 可能与较高的交叉用药率有关[37]。

综合现有研究可见, 目前氢化可的松治疗早产儿低血压的剂量尚无统一标准, 加拿大一项调查显示, 新生儿科医师实际使用氢化可的松剂量范围波动较大, 通常为 1~5 mg/kg/d [38]。尽管病情严重的早产儿可能需要更高剂量, 但剂量与不良预后之间的关联仍需深入探究, 因此临床实践中必须严谨选择氢化可的松的剂量, 权衡治疗获益与潜在风险。

4. 氢化可的松的药物不良反应

4.1. 消化系统不良反应

尽管氢化可的松的临床有效性已得到诸多证实, 但其潜在安全风险仍需重视, 尤其是在自发性肠穿孔与感染风险方面。既往开展的两项随机对照试验因试验组的新生儿自发性肠穿孔风险增高而提前终止[24][28], 回顾性分析表明, 该风险可能与氢化可的松的使用及早期联用吲哚美辛存在叠加效应相关[39]; 与此同时, 另一项禁止早期使用布洛芬的试验表明, 早期使用低剂量氢化可的松并未增加自发性肠穿孔的发生率, 但试验组患儿的晚发败血症发生率有所上升, 且这一现象在胎龄 24~25 周的亚组中表现尤为突出[25]。

4.2. 神经系统不良反应

氢化可的松对早产儿远期神经发育的影响是当前临床应用中备受关注且存在争议的核心问题。动物实验研究表明, 单独使用选择性糖皮质激素治疗时, 因脑部盐皮质激素受体持续空缺可导致神经元凋亡, 而同时给予皮质醇则能抑制该细胞凋亡过程, 此现象可能源于氢化可的松同时具有盐皮质激素和糖皮质激素活性, 使其相较于地塞米松等选择性糖皮质激素类似物具有更安全的神经学风险[40]-[42]。临床研究层面, 多项研究呈现积极趋势: 一项系统评价指出, 氢化可的松可显著降低死亡或主要神经感觉障碍风险[8]; 另一项荟萃分析则证实, 其对存活者脑瘫结局无显著不良影响[33]; 对 PREMILOC 试验患儿的 5 岁结局数据进行分析发现, 氢化可的松可能在儿童期的工作记忆、信息保持能力、发育和发展等方面具有潜在益处[43]。神经影像学研究同样提供了支持证据, 早期氢化可的松暴露既未显著增加脑白质损伤或中重度脑损伤的发生率[44], 也未引起主要脑区白质微结构或神经环路的显著改变[45]。但需注意的是, 尽管现有研究结果偏向有利, 但目前所有针对预防性使用氢化可的松的随机对照试验, 在试验设计或统计效能上均不足以检测出可能存在的、虽微小但具有临床意义的神经发育差异[46][47]。因此, 越多越多

研究者呼吁针对早期氢化可的松疗法的远期神经发展结局开展更深入的研究[48] [49]。

4.3. 其他系统不良反应

氢化可的松引起其他系统不良反应亦不容忽视。其使用可导致高血糖, 同时通过影响水盐及电解质平衡, 引起水钠潴留、低钾血症、高钠血症及钙磷排泄增加, 进而诱发水肿、高血压、骨矿化不良甚至肾钙质沉着等并发症[18]。Watterberg 等的研究指出, 晚期使用氢化可的松会增加新发高血压及需降压药物治疗的风险, 同时高血糖发生率也显著升高[50]; STOP-BPD 试验也报告了类似结果, 该试验中氢化可的松使用组高血糖(包括需胰岛素治疗的高血糖)风险增加[51]。此外, 氢化可的松使用可抑制蛋白质合成与骨形成, 并促进骨钙流失, 可能导致肌肉萎缩、生长迟滞及骨质疏松性骨折等的风险增高[19]。

5. 未来展望

极/超早产儿因 HPA 轴发育不成熟, 容易发生 TAP, 氢化可的松凭借其独特的药理特性, 在稳定血流动力学、预防 BPD、提高无 BPD 存活率及降低出院前死亡率等方面展现出临床价值, 但同时可能增加胃肠道穿孔等不良反应的风险, 因此, 其使用必须基于个体化的风险与获益评估。在临床应用中, 应在明确用药目的基础上, 综合评估患儿胎龄与出生体重、病情严重程度、循环情况及合并症, 并结合医疗机构的监测与管理条件, 实施个体化治疗及动态调整。

近年来相关研究不断增加, 但现有证据仍有限, 目前仅有一项大型随机对照试验报告了其使用的临床获益及 5 年随访的安全性数据, 因此现行临床指南对预防性氢化可的松使用仍持谨慎态度。未来研究亟需围绕适用人群的风险分层、最佳剂量与给药方案、对脑结构与神经发育的长期影响, 以及其他重要远期安全性结局等关键科学问题开展高质量研究, 以期极/超早产儿氢化可的松的早期合理应用提供更为明确和可靠的循证依据。

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