

低浓度阿托品滴眼液在近视防控中的研究进展

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摘要

近视已成为全球重大公共卫生问题, 预计到2050年全球近视人口将占总人口的一半, 近视防控工作迫在眉睫。低浓度阿托品滴眼液作为目前唯一经循证医学验证能有效延缓近视进展的药物, 近年来受到广泛关注。然而, 最佳浓度选择、长期用药安全性、个体化治疗策略及预防应用价值等问题仍需进一步研究明确。因此, 本文系统综述了低浓度阿托品滴眼液防控近视的作用机制、临床应用有效性、不同浓度的选择策略、联合治疗方案以及安全性与不良反应, 旨在为临床合理应用提供参考。

关键词

近视, 近视防控, 低浓度阿托品, 联合治疗, 安全性

Research Progress on Low-Concentration Atropine Eye Drops in Myopia Prevention and Control

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Abstract

Myopia has become a significant global public health concern, with projections indicating that myopic individuals will account for approximately half of the world's population by 2050. Consequently, the prevention and control of myopia progression has emerged as an urgent priority. Low-concentration atropine eye drops currently represent the only pharmacological intervention with evidence-based validation for effectively slowing myopia progression, and have garnered substantial attention

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in recent years. Nevertheless, several critical issues remain to be elucidated, including optimal concentration selection, long-term medication safety, individualized therapeutic strategies, and the prophylactic value in premyopic children. Accordingly, this article systematically reviews the mechanisms underlying low-concentration atropine in myopia control, clinical efficacy, concentration-dependent selection strategies, combination therapeutic regimens, as well as safety profiles and adverse reactions, with the aim of providing evidence-based guidance for rational clinical application.

Keywords

Myopia, Myopia Prevention and Control, Low-Concentration Atropine, Combination Therapy, Safety

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1. 引言

近视是全球范围内最常见的眼科疾病之一,尤其在儿童和青少年群体中呈现发病率逐年上升、发病年龄低龄化、高度近视占比增加的趋势[1]。根据 Holden [2]等的预测,至 2050 年全球近视患病率将达到 49.8%,其中约 1/10 为高度近视。一项荟萃分析研究估计我国目前近视患病率为 33.6%,预计 2050 年可高达 61.3% [3]。高度近视可引发脉络膜新生血管、黄斑裂孔、视网膜脱离等严重并发症,导致不可逆的视力损害,给个人、家庭和社会带来沉重负担[4] [5]。因此,预防近视发生、延缓近视进展、防治病理性近视已成为我国眼科公共卫生领域的重点工作。

近视防控手段主要包括光学矫正和药物调控两大类。光学矫正包括传统单焦框架眼镜、角膜塑形镜(orthokeratology, OK 镜)、多区正向光学离焦镜片等;药物调控则以低浓度阿托品滴眼液为核心代表[6]。自 20 世纪 70 年代开始,阿托品滴眼液在近视防控中的应用已有数十年历史。高浓度阿托品虽控制效果显著,但畏光、视近模糊、停药反弹等不良反应严重限制了其临床应用[7] [8]。近年来,随着 ATOM (Atropine for the Treatment of Myopia) [9]、LAMP (Low-concentration Atropine for Myopia Progression) [10] [11]等大样本、前瞻性临床研究结果的公布,低浓度阿托品(一般指浓度 $< 0.1\%$)因其良好的疗效和安全性,成为近视防控领域的研究热点。本文基于最新研究进展,系统综述低浓度阿托品滴眼液在近视防控中的研究现状,以期为临床实践和未来研究提供参考。

2. 作用机制

低浓度阿托品控制近视进展的确切机制尚未完全阐明,但其并非通过单一的调节麻痹途径发挥作用,而是涉及多靶点、多通路的复杂调控网络[12]。早期研究认为阿托品通过阻断睫状肌 M 受体、放松调节来控制近视进展。然而,McBrien 等[13]的研究表明阿托品可在未引起瞳孔散大及改变调节功能的情况下显著抑制眼轴增长。提示存在非调节机制参与近视控制。目前认为阿托品通过作用于眼后段组织的 M 受体发挥近视防控作用[12] [14]。如视网膜色素上皮、脉络膜或巩膜组织[15] [16]。但针对胆碱能通路,Thomson 等[17]的研究表明胆碱能过度活跃不是近视发生的基础,并由此质疑阿托品是否通过胆碱能拮抗来抑制近视进展。此外,既往研究提示非胆碱能受体途径也协同参与近视控制。如阻断 α_2 肾上腺素能受体激活[18]、增加视网膜多巴胺的释放[19]、通过一氧化氮(NO)途径[20]、增加脉络膜血流[21]等发挥作用。这些研究表明,阿托品的近视控制效应机制复杂,但暂未形成统一意见。其可能源于多靶点、多通路的协

同作用, 涉及神经递质调控、生长因子信号抑制、血流动力学改变等多方面, 仍需更多基础研究进行探索。

3. 低浓度阿托品的临床应用

3.1. 临床有效性

低浓度阿托品滴眼液是经循证医学验证能有效延缓近视进展的药物[22]。其临床有效性主要通过等效球镜度(spherical equivalent, SE)延缓率和眼轴长度(axial length, AL)增长延缓率来评估。目前已经有大量临床研究证明了低浓度阿托品对近视防控的有效性[8] [23] [24]。其中较为经典的新加坡 ATOM1 [7]研究纳入 400 例 6~12 岁近视儿童, 发现 1%阿托品治疗 2 年可使近视进展减少约 77%。LAMP 研究纳入 438 例 4~12 岁儿童, 比较 0.05%、0.025%、0.01%阿托品与安慰剂。第一阶段(1 年)结果显示近视控制效果呈浓度依赖性: 0.05%阿托品在 SE 进展延缓(66%)和 AL 增长延缓(51%)方面均最优, 0.025%次之(43%和 29%), 0.01%再次之(36%和 22%), 均显著优于安慰剂[10]。第二阶段(2 年)和第三阶段(3 年)持续证实 0.05%阿托品的优越性, 且 0.01%阿托品疗效约为 0.05%的一半[25] [26]。第四阶段报告指出持续 5 年给予 0.05%阿托品, 近视控制效果持续有效且安全性良好[27]。国内的临床研究也提供了重要证据[28] [29]证实了低浓度阿托品对近视控制的有效性。除了对已经近视儿童延缓近视进展存在疗效, LAMP2 研究[11]同样发现在 4 至 9 岁无近视的儿童中, 每晚使用 0.05%阿托品眼药水与安慰剂相比, 2 年后近视的发生率显著降低, 且快速近视进展的患儿比例也较低。He 等[30]的研究也支持低浓度阿托品对近视前期患儿控制近视发生的良好作用。提示低浓度阿托品在预防近视发生及控制近视进展方面均有效。

3.2. 不同浓度低浓度阿托品的应用

低浓度阿托品的最佳治疗浓度仍存在学术争议, 从 0.01%~0.1%浓度均有不同的研究结论[8] [31]。综合现有证据, 0.05%阿托品在亚洲人群中表现出最强的近视控制效果, 且长期应用安全性良好, 被认为是平衡疗效和安全性的最佳浓度之一[8] [10] [26] [27] [32]。0.01%阿托品虽然疗效相对较弱, 但不良反应最少、反弹效应最低、患者耐受性和依从性最佳[24] [33], 且已获得我国国家药监部门正式批准, 可作为基础用药浓度。对于应答不佳或近视进展快速的儿童, 可考虑提高浓度至 0.02%或 0.05%。此外, 年龄和初始近视程度是影响治疗应答的重要因素。Li 等[34]的分析显示, 在 0.05%、0.025%和 0.01%等不同浓度的研究中, 年幼儿童需要最高的 0.05%浓度才能实现与接受较低浓度的年长儿童类似的近视进展控制。LAMP2 研究[11]同样发现 0.05%阿托品在 4~9 岁非近视儿童中可有效降低近视发病率, 而 0.01%效果不显著, 提示低龄儿童可能需要更高浓度。临床实践中, 可参考“阶梯式”用药策略: 以 0.01%起始, 根据应答情况调整浓度[35]。

3.3. 联合其他防控方式

由于单一手段控制近视效果有限, 联合治疗成为重要发展方向。低浓度阿托品与光学矫正手段联合可产生机制互补的协同增效作用[36] [37]。角膜塑形镜(OK 镜)通过夜间佩戴改变角膜形态, 暂时性降低近视度数并矫正裸眼视力, 其控制近视机制与阿托品不同(主要为周边离焦效应)。两者联合可从不同途径抑制眼轴增长, 产生协同效应。多项研究证实联合治疗的优越性。Kinoshita 等[38]的 2 年随机对照试验显示, 0.01%阿托品联合 OK 镜较单用 OK 镜更有效减缓眼轴增长, 尤其对近视度数较低儿童效果明显。Wang 等[39]的回顾性研究发现, 联合治疗组 2 年 AL 变化(0.12 ± 0.08 mm)显著优于单用 OK 镜组(0.21 ± 0.09 mm), 且不会增加不良反应。Meta 分析也提供了高级别证据。Tsai 等[40]纳入 19 项随机对照研究进行 Meta 分析, 研究提示 0.01%阿托品联合 OK 镜的近视控制效果显著优于单用 OK 镜或单用 0.01%阿托

品。除了 OK 镜, 联合离焦框架眼镜(DIMS 镜)同样广泛应用。DIMS 镜基于视网膜周边离焦理论设计, 通过特殊多焦点镜片使佩戴者在看远和看近时均保持一定程度的离焦状态, 抑制眼轴过度增长[41]。其与阿托品联合同样可产生协同效应。Huang 等[42]的研究显示, DIMS 镜联合阿托品在延缓眼轴和近视进展方面, 较单用 DIMS 镜和单用单焦框架镜有更好的疗效。Tang 等[43]比较了单用 OK 镜、单用 DIMS 镜、0.01%阿托品联合 OK 镜、0.01%阿托品联合 DIMS 镜四种方案, 发现两种联合治疗均较单用效果更好, 0.01%阿托品联合 OK 镜的 AL 控制效果略优于联合 DIMS 镜。对于临床决策选择哪种治疗方案, 总结以下表格(表 1)供读者交流。

Table 1. Clinical reference for low-concentration atropine eye drops
表 1. 低浓度阿托品滴眼液临床使用参考

临床情景	推荐方案	考虑因素
6~10 岁, 快速进展(>0.75 D/年)	0.05%单药或 0.01% + OK 镜	最强控制, 需密切监测副作用
10~12 岁, 中速进展(0.5~0.75 D/年)	0.01%起始, 应答不佳提高浓度	平衡疗效与长期安全性
≥13 岁, 慢速进展(≤0.5 D/年)	0.01%单药或观察	自然进展减缓, 避免过度干预
2 年以上稳定, ≥13 岁	评估停药, 逐渐减量	密集监测反弹, 阈值 0.50 D/半年
应答不佳(>0.75 D/年)	升级浓度或联合治疗	排除依从性因素后强化
角膜不适合/经济受限/年龄 < 8 岁	0.05%单药或 0.01% + DIMS	避免 OK 镜限制因素
调节功能低下/浅色素虹膜	降低浓度或 DIMS/OK 镜单用	减少抗胆碱能副作用

4. 安全性和不良反应

低浓度阿托品的不良反应呈浓度依赖性, 随着浓度降低, 不良反应显著减少[8] [44]。主要不良反应包括: 1) 瞳孔散大与畏光: Fu 等[45]发现使用 0.01%和 0.02%阿托品用药后瞳孔较用药前分别散大 0.69 ± 0.39 mm、 0.78 ± 0.42 mm, 用药 4 个月后趋于稳定, 停药 2 个月后恢复如初。2) 调节能力下降与近视力下降: 0.01%阿托品使调节幅度平均下降 1.61 ± 0.31 D [45]。0.01%阿托品近视力下降发生率约 2.3%, 高浓度可达 11.9% [44]。3) 过敏反应: 多见于阿托品过敏者, 常在用药 2 周内发生, 表现为眼部瘙痒、灼热、眼睑肿胀和眼周发红等[46]。出现过敏反应应立即停药, 一般 24 h 后症状减轻, 1 周恢复, 局部糖皮质激素使用可加速恢复。4) 眼部刺激性反应: 少数儿童出现眼部刺痛不适[44]。5) 全身不良反应: 0.01%阿托品全身不良反应罕见。迄今为止, 在长达 5 年的前瞻性研究[47]及停药后 10 年以上的随访研究[9]中, 均未发现与药物使用相关的严重全身不良反应。

长期用药安全性是临床关注重点。ATOM2 研究[47]与 LAMP 研究[27] 5 年结果均提示 0.01%阿托品长期应用有效且安全。ATLAS 研究[9]对停药后 10~20 年的成年患者评估未发现近视相关眼部并发症增加, 且发现脉络膜厚度增加的潜在长期益处。一项研究[48]报道使用至少 5 年阿托品滴眼液的近视患儿与未使用阿托品的相比, 在白内障、原发性开角青光眼和黄斑病变的发生率无差异, 提示阿托品长期使用并不会增加眼部并发症的风险。除此外, 停药后反弹效应是评估长期疗效的重要指标, 浓度越低, 反弹效应越小, 0.01%阿托品表现出最低的反弹效应[49] [50]。CHAMP3 研究[33]显示在持续治疗 3 年后停药, 0.01%硫酸阿托品眼药水在近视进展方面表现的反弹效应可忽略不计。同时, 针对逐渐停药与突然停药, 对于 0.01%阿托品滴眼液应答良好(进展不超过 0.25 D), 可考虑停药并密切观察反弹效应; 对于年龄小、近视进展快、应答一般的儿童青少年, 可继续用药来维持更好的近视防控效果[49]。然而, 近期一项荟萃分析[51]纳入了 33 项随机对照试验, 研究平均随访时间为 19.5 ± 12.3 个月, 而更长疗程(>10 年)的安全

性数据仍有限, 需持续积累。

不良反应处理策略: 对于轻度不良反应(畏光、近视力下降、刺激性反应), 能耐受者可暂时观察; 不耐受者可对症处理: 畏光可戴遮阳帽、变色眼镜; 视近不清晰可验配眼镜附加眼镜或进行调节功能训练。出现过敏反应应立即停药, 必要时局部应用糖皮质激素。严重不良反应或轻度不良反应不能耐受者, 建议停用并更换其他防控方式。

5. 总结和展望

低浓度阿托品滴眼液作为近视防控的一线药物, 其疗效已获广泛循证医学证据支持。低浓度阿托品延缓近视进展效果呈浓度依赖性; 0.01%阿托品安全性最佳、反弹最小, 适合作为基础用药; 0.05%在亚洲人群中疗效最优, 可作为快速进展近视的优先选择; 联合 OK 镜或 DIMS 镜可产生协同增效, 是提升防控效果的重要策略。然而, 当前仍存在诸多挑战与未解问题, 未来研究方向可聚焦于以下方面: 1) 开发选择性 M1/M4 受体拮抗剂或局部缓释制剂, 在保留巩膜-脉络膜靶点效应的同时, 减少虹膜括约肌和睫状肌的脱靶作用, 从根本上降低不良反应发生率。2) 开展前瞻性队列研究, 整合基线脉络膜厚度(SFCT)、脉络膜血流灌注(OCT-A)、眼轴长度/角膜曲率比(AL/CC ratio)等构建疗效预测模型, 实现“先验式”浓度选择而非“试错式”调整。3) 建立全国性真实世界登记数据库, 追踪 > 10 年用药者的晶状体混浊发生率、视网膜功能、眼压变化、全身暴露量(血药浓度监测), 以及成年后的视觉质量和生活质量结局。随着低浓度阿托品在近视防控工作中的更加广泛应用, 希望为全球数亿近视儿童带来更光明的未来。

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