TFOS DEWS III 管理与治疗报告

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• 摘要: **本报告基于循证医学，综述了当前干眼病(DED)的治疗策略.干眼病的一线治疗主要聚焦于泪液补充,保存和刺激泪液分泌，尤其是泪液补充剂，这些仍是干眼病治疗的基石.睑板腺功能障碍 (MGD) 作为干眼病的主要病因，通常采用热敷及多种门诊治疗手段，包括设备驱动的眼睑加热技术,强脉冲光治疗,低强度光疗法及其他新兴技术.睑缘清洁治疗则包括睑缘清洁湿巾,抗螨形螨治疗,睑缘去角质术及局部抗生素的应用.**

部分病因导致的干眼病可采用包括皮质类固醇,局部T细胞免疫调节药物及多种药理制剂的抗炎治疗，以及生物性泪液替代物(如自体血清和富血小板血浆)治疗.经鼻神经刺激的神经调节及新型药物治疗，为未来干眼病的治疗提供了更多选择.对于严重或难治性病例，羊膜移植和复杂手术方法等进阶治疗可提供解决方案.生活方式调整(包括改善眨眼习惯,膳食补充和环境调节)在干眼病的长期管理中发挥重要作用.患者教育及对治疗的依从性对干眼症状的缓解同样至关重要.

TFOS DEWS III 治疗指南提供了一个循证框架，帮助临床医生根据不同病因选择相应干预措施，以实现针对不同类型干眼病的精准管理. (Am J Ophthalmol 2025;000: e1–e78.

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缩略词

CMC	Carboxymethylcellulose, 羧甲基纤维素;
CsA	Cyclosporine, 环孢素;
DED	Dry eye disease, 干眼病;
DEWS	Dry eye workshops, 干眼病工作组;
FDA	Food and Drug Administration, 美国食品和药物监督管理局;
HP-guar	Hydroxypropyl guar, 羟丙基瓜尔胶;
HA	Hyaluronic acid, 透明质酸;
IL	Interleukin, 白细胞介素;
IPL	Intense pulsed light, 强脉冲光;
LASIK	Laser-assisted in situ keratomileusis, 准分子激光原位角膜磨镶术;
LLT	Lipid layer thickness, 脂质层厚度;
LLLT	Low-level light therapy, 低强度光疗法;
MGD	Meibomian gland dysfunction, 睑板腺功能障碍;
MMP	Matrix metalloproteinase, 基质金属蛋白酶;
NGF	Nerve growth factor, 神经生长因子;
NIBUT	Non-invasive breakup time, 非接触泪膜破裂时间;
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells, 活化B细胞的核因子kappa-轻链增强子;
OSDI	Ocular Surface Disease Index, 眼表疾病指数量表;
PEG	Polyethylene glycol, 聚乙二醇;
PRGF	Plasma rich in growth factors, 富含生长因子血浆;
PRP	Platelet-rich plasma, 富血小板血浆;
PUFA	Polyunsaturated fatty acids, 多不饱和脂肪酸;
RCT	Randomized controlled trial, 随机对照试验;

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rhPRG4	Recombinant human proteoglycan 4, 重组人蛋白多糖4;
ROS	Reactive oxygen species, 活性氧;
SANDE	Symptom Assessment iN Dry Eye (questionnaire), 干眼症状评估问卷;
SDP-4	Silk-derived protein-4, 丝源蛋白4;
SPEED	Standard Patient Evaluation of Eye Dryness (questionnaire), 标准干眼症状评估问卷;
TBUT	Tear breakup time, 泪膜破裂时间;
TFOS	Tear Film & Ocular Surface Society, 国际泪膜与眼表学会;
TMH	Tear meniscus height, 泪河高度;
TRPM8	Transient Receptor Potential cation channel subfamily M member 8, 瞬时受体电位M8离子通道;
TTO	Tea tree oil, 茶树油;
UCS	Umbilical cord serum, 脐带血请

报告目标

本报告旨在对干眼病患者管理和治疗的最新文献进行全面概述, 并基于国际泪膜与眼表学会 (TFOS) 干眼病专家共识 (DEWS)III 的最新亚型分类标准, 结合患者的临床表现和诊断结果, 制定循证治疗策略, 以指导临床医生合理选择治疗时机[1].本报告重点关注自上一版TFOS DEWS II《管理与治疗报告》发布以来的最新证据[2].由于部分治疗方法的作用机制存在交叉(例如某些药物兼具抗炎,抗菌及改善眼睑异常等多重作用), 所列治疗方案可能与其他治疗领域重叠.本报告最终目标是明确现有证据是否支持将所列举的治疗方案用于TFOS DEWS III《诊断方法学报告》中更新的一种或多种类型干眼病[1].

生活方式建议

生活方式因素在干眼病的发生和发展中均起关键作用, 不仅影响眼部健康, 还关乎患者的整体幸福感和生活质量[3,4].现代行为习惯, 包括睡眠不足[5–10],使用化妆品[11],眼部和眼周手术的选择[12]以及全身用药[9,12], 都可能引发或加重干眼症状, 导致眼部不适,视力障碍和日常功能下降.

电子设备过度使用是导致干眼病最重要的生活方式因素之一[9,13,14].长时间注视屏幕引起的眨眼频率减少和不完全眨眼, 会导致泪膜不稳定,泪液蒸发增加和眼表损伤[14].这种长期不适常导致情绪低落,疲劳和工作效率下降, 从而对心理健康产生负面影响.饮食同样会影响干眼病的严重程度.富含ω-3脂肪酸的饮食(如鱼类和亚麻籽)有助于改善泪液质量并减轻炎症反应.相反, 深加工食品和低必需营养素的饮食可能导致全身性炎症反应, 加重眼表疾病[9,15–18].

干眼症状的累积不仅造成躯体不适, 还可能影响情绪健康,社交活动和生活质量[3,19].慢性干眼病患者更易患有严重的焦虑和抑郁[20–24], 这可能与持续的眼部刺激和视力障碍影响了日常活动有关[5,25].

环境条件会影响眼表健康并可能导致干眼病. TFOS生活方式报告已对此进行了全面阐述[26], 包括气候因素(阳光,温度,湿度,风速和蒸汽),污染物和过敏原.这些因素可直接作用于眼表引起即时不适感, 也可以通过间接途径对眼表产生影响, 如紫外线辐射导致翼状胬肉(其物理存在会破坏泪膜的稳定性, 详见第11.1.4节).

具体的生活方式调整建议包括:

避免诱发干眼症状的因素:虽然难以完全避免, 但对于已知会加重干眼病的特定因素, 如长时间阅读或通风过强的环境, 应予以规避[26].

局部环境控制:使用简单的USB驱动桌面加湿器可提高局部空气湿度, 改善泪膜稳定性和主观舒适度[27,28].湿房镜也具有类似效果[29].

物理防护:侧边防护眼镜可阻挡气流和蒸汽对眼睛的直接刺激, 但目前研究仅证实其与提高眼周湿度联合使用时的效果[30].湿房镜(详见第6.2.2节)能有效减少泪液蒸发[31],眼表和污染物的接触, 同时增加佩戴者面部周围空气湿度, 可显著改善眼表状态[32]和泪膜质量, 缓解干眼症状[33].值得注意的是, 一项研究发现使用软性接触镜进行五年以上的紫外线防护并未明显改善眼表状况, 尽管该研究未评估泪膜变化[31].

通过认识到生活方式,干眼症状和生活质量之间的深刻联系, 临床医生能够引导患者做出可持续的生活方式调整, 以实现症状的长期缓解并提升幸福感.近期一项研究表明, 笑对干眼病具有治疗作用, 其在症状和体征改善方面的效果优于局部使用 0.1% 透明质酸(HA)[34].通过有意识地调整生活方式, 如定时离屏休息,改善营养和保持良好睡眠习惯, 可显著缓解干眼症状, 同时改善眼部和整体健康状况.无论患者属于何种类型的干眼病, 也无论针对其临床表现拟采取何种治疗方案, 都应考虑将这些生活方式调整纳入管理策略.

泪液分泌不足

- 泪液补充:

泪液补充剂与稳定剂

泪液补充剂是增强和/或稳定泪膜的药物, 也是应对泪液不足或功能障碍的核心治疗手段之一, 适用于各种病因引起的干眼病[35].这些疗法在许多情况下通过稳定泪膜, 达到恢复眼表微环境稳态的目的, 可以最大限度地减少 “干眼病恶性循环”, 即泪膜不稳定,高渗状态,炎症和上皮损伤的循环持续[36–38].

这类产品旨在模拟天然泪膜的组成, 但通常缺乏天然泪膜中含有的生物活性成分[39].尽管可以列出泪液补充剂和稳定剂中可能含有的 “活性” 成分, 但其疗效往往并非由单一成分决定, 且 “活性” 成分的定义可能因不同地区的监管标准而异.例如在美国, 非处方泪液补充剂中可能含有重要的辅料, 但由于产品仅允许列出包含在美国食品药品监督管理局(FDA)清单中的活性成分, 这些辅料常未被明确标注.此外, 某些配方可能包含两种活性润滑剂以及“非活性聚合物”, 这些成分在眼表润滑,泪

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液留存和保湿方面发挥着独特而重要的作用.因此, 产品的整体配方,组成及各成分间的相互作用方式才是影响其性能的关键因素.此外, 还需综合考虑是否含防腐剂及其给药系统的设计.

如前所述[2,40–44], 泪液补充剂的成分较为复杂, 主要包括以下类型:

增粘剂:通常为针对水液缺乏型干眼病的含水配方, 包括卡波姆940,羧甲基纤维素 (CMC) ,右旋糖酐,羟丙基瓜尔胶(HP-guar),羟丙基甲基纤维素,聚乙烯醇,聚乙烯吡咯烷酮和聚乙二醇(PEG).

仿脂质制剂:针对蒸发过强型干眼病, 可降低泪膜表面张力, 使泪液更均匀地分布于眼表[39].所含脂质成分(详见第6.1.1.5节)包括:磷脂,甘油三酯,饱和与不饱和脂肪酸,矿物油,蓖麻油,椰子油和卵磷脂[40–43,45,46].其中磷脂可呈中性(两性离子), 也可带负电(阴离子)或带正电(阳离子).

泪膜稳定剂(全氟己基辛烷):该成分在美国归类为处方药物, 在其他地区则归类为医疗器械[47–50].

透明质酸(HA):作为泪液补充剂中日益常见的成分, 这种天然存在的糖胺聚糖广泛分布于人体各组织, 包括滑液,玻璃体及房水中.研究表明, 在动物实验中, 高分子量透明质酸制剂对干眼病的治疗作用比低分子量制剂效果更佳[51], 体外实验还显示其具有抑制角膜细胞凋亡和炎症的作用[52].更多详细信息参见第 6.1.1.2节.

防腐剂:包括苯扎氯铵和乙二胺四乙酸在内的防腐剂常用于防止滴眼液被细菌污染.然而, 苯扎氯铵等防腐剂可能具有毒性和促炎作用, 加剧干眼病[53,54].因此, 目前趋势正转向使用单包装无防腐剂制剂, 或采用毒性更低的防腐剂(如稳定氯氧复合物 Purite®)[55,56]或过硼酸钠(GenAqua®;美国Alcon公司; Dequest®)[57], 以及采用特殊设计的可多次使用的,防污染的无防腐剂瓶[58].另一种长期使用的防腐剂是聚季铵盐-1(Polyquad®;美国Alcon公司)[57].这是一种杀菌性季铵化合物, 在泪液补充剂中的浓度为 0.001%.研究表明, 该浓度下即使经过24小时暴露, 也不会对培养的人角膜上皮细胞的细胞动力学,形态或有丝分裂活性产生不良影响[59].

低渗剂旨在中和干眼病患者泪膜的高渗透压[60].

渗透压保护剂通过优化细胞健康状态, 帮助眼表组织抵抗泪液高渗和炎症的影响[61–63].常用成分包括 L-肉碱,赤藓糖醇,海藻糖(见 6.1.1.7 节),甜菜碱,山梨糖醇和甘油[43].

辅料

缓冲剂:(如碳酸氢盐,磷酸盐,柠檬酸盐,硼酸盐)用于维持泪膜的正常pH值(7.4)[2,53,58].

盐类用于调节渗透压.

以下内容将综述各类泪液补充剂的配方特点, 重点介绍自 TFOS DEWS II 报告[2]发布以来取得的新研究进展.

瓜尔胶类补充剂. HP-guar 是一种高分子聚合物, 其主链化学结构可在眼表形成高粘度凝胶.羟丙基基团通过阻断分子间氢键作用, 既提高了瓜尔胶的溶解性, 又能通过羟丙基基团优先结合于糖萼层受损区域的疏水区[64].在Systane®(美国 Alcon 公司)的配方中, 硼酸盐作为缓冲剂, 可与 HP-guar 的顺式二醇共价交联, 形成粘弹性凝胶[65].这种 HP-guar 增粘聚合物与润滑剂协同作用, 能在眼表形成水合支架, 防止脱吸附, 提供长效保护[66]. HP-guar 与硼酸盐的原位交联具有独特优势, 其作用机制与泪膜生理 pH 值相匹配[66], 生成的凝胶通过眼表泪膜生理pH环境促进润滑剂滞留[67].临床研究证实, 含 HP-guar 的补充剂(联合聚乙二醇和/或丙二醇)可显著提升泪膜稳定性并提供持久润滑效果[68], 同时能降低泪液渗透压,减少角膜荧光素钠染色, 全面改善眼表健康[69].此外, 该配方还可增加杯状细胞密度, 并通过形成保护层促进上皮修复, 防止眼表进一步损伤, 从而支持表层上皮细胞再生[70].

含透明质酸的泪液补充剂. 透明质酸(HA)是一种天然存在的带有负电荷的非硫酸化糖胺聚糖, 广泛分布于人体细胞外基质中, 是滑膜液的主要成分之一.其分子量可高达数百万道尔顿, 具有促进细胞增殖和迁移的功能.在泪液补充剂中, HA通过增加粘度和提供润滑发挥作用.HA表现出非牛顿流体的剪切稀化特性, 即其粘度随剪切速率变化而变化[71,72].这种特性与其分子量密切相关[73].小鼠干眼病模型研究表明, 与低分子量HA或地夸磷索滴眼液相比, 高分子量HA能显著延长泪膜破裂时间并降低丽丝胺绿染色评分[51].

一项系统综述纳入了53项HA治疗干眼病的临床试验(含8项安慰剂对照研究)[74].研究使用的HA浓度为0.1%-0.4%, 疗程4周至3个月, 结果一致显示HA能安全有效地改善干眼病体征和症状.但现有研究尚未明确最佳给药频率,制剂配方和透明质酸浓度.

另一项涵盖21项随机试验的文献综述比较了HA与其他17种单一成分干眼病治疗药物的效果[75].结果显示多数眼表和泪膜指标在组间无显著差异, 这表明可能各治疗方法效果相当, 或因研究样本量不足导致研究效能不足.此外, 也可能与给药频率未优化(每日剂量在1 - 8滴之间)或使用的 HA 浓度过低, 无法达到治疗水平有关.

一项纳入 18 项研究并进行 Meta 分析的系统综述比较了HA与非 HA 类泪液补充剂, 结果显示含 HA 的泪液补充剂在改善眼表染色及患者症状方面更具优势[76].然而, 通过 Schirmer 试验测量的泪液分泌量及通过 TBUT 评估的泪膜稳定性, 在不同治疗组间并无显著差异.

一项大型多中心研究评估了将 CMC 与 HA 联合的泪液补充剂(每日 2 次, 持续 90 天)相较于单纯 CMC 的有效性和安全性[77].结果显示与基线相比, 两组患者的自述症状及临床医生测量的眼表和泪膜参数均显著改善, 但组间结局差异较小.

HA可通过多种方式进行修饰以改善其性能, 如调整分子量,粘度和疏水性等.对分子特定区域进行交联可增强其抗降解能力并提高生物利用度[78].

黄原胶. 黄原胶是从野油菜黄单胞菌中提取的高黏度多糖分子[79].其特性与泪液相似, 包括随剪切速率增加而黏度降低的特点, 且在温度,生物聚合物浓度,盐浓度及 pH 值等方面也具有相似性[79].这些特性使黄原胶能够作为眼科药物的载体, 延长药物在眼表的停留时间[80].在干眼病研究中, 黄原胶的效果已与 CMC [79]及聚乙二醇/丙二醇(PEG/propylene glycol)[81] 进行对比.此外, 黄原胶与其他成分联合使用的抗氧化和渗透保护作用已在体外实验和兔模型中得到评估[82].

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在一项纳入15名干眼病患者的研究中, 评估了0.2%黄原胶的治疗效果.结果显示, 与 CMC 相比, 每日四次使用黄原胶持续一个月可显著改善杯状细胞参数,结膜细胞学特征和角膜染色情况, 但研究同时也报告了 Schirmer I结果的降低[79].另一项III期多中心 RCT 研究纳入了148名干眼病患者, 比较了0.09%黄原胶联合0.1%硫酸软骨素(每日四次, 持续60天)与聚乙二醇/丙二醇 (PEG/propylene glycol) 的疗效[81].研究发现两种治疗方案在改善临床指标方面效果相似, 包括 Schirmer 试验值, TBUT 和眼部舒适度等[81].

一项针对 30 名干眼病患者的前瞻性多中心临床研究, 评估了一种含 0.2% 黄原胶与 0.025% 地塞米松磷酸钠的无防腐剂滴眼液(每日 3 次)的疗效 [83].结果显示, 与基线相比, 该配方在治疗 1 个月后可显著减轻眼部充血, 同时显著延长 TBUT, 明显改善角膜和结膜染色.此外, 该溶液还能缓解干眼症状, 且表现出良好的安全性.

聚合物组合配方. 据报道, 包含具有抗炎特性(如黄原胶和瓜尔胶)的多聚合物配方, 有助于减轻炎症并促进上皮愈合[84,85].常用组合之一为HP-guar与HA.一项评估该聚合物组合临床前及临床效应的系统综述总结了其保湿,润滑和锁水能力[86].在体内角膜损伤模型中, HP-guar＋HA 显著加速了角膜上皮再生, 效果优于其他基于 HA 的滴眼液[87].

临床试验强调, 这种双聚合物润滑滴眼液组合可减轻干眼病的临床症状与体征, 改善 TBUT, 并延长其在眼表的停留时间[88,89].在一项针对白内障术后患者的回顾性研究中, 双聚合物配方可减轻干眼症状和角膜损伤, 尤其在术前使用时效果更显著[90].在健康人群中, HP-guar+HA 滴眼液可显著提升泪膜质量, 同时延长 TBUT 并增加泪河高度 (TMH) [91].此外, 对于数码产品使用者, 该双聚合物成分可显著改善眼部舒适度,提升生活质量[92].

临床研究表明, 含聚合物组合的泪液补充剂在缓解干眼症状,维持泪膜稳定性及患者满意度方面优于单一聚合物配方[77,93,94].例如, 一项对比HA+CMC 组合滴眼液与单纯 CMC 产品的 RCT 研究显示, 双组分治疗组的 OSDI 评分和 TBUT 改善更为显著[77].另一项研究报道, 每日 3 次持续使用含PEG和丙二醇的泪液补充剂90天后, 可显著提高杯状细胞密度, 并改善角膜和结膜染色情况[70].

含脂质泪液补充剂. 脂质乳剂型泪液补充剂的临床应用日益广泛[40–43,45,46,95,96].与非脂质制剂相比, 含脂质配方在短期[46,97]和长期[98–100]观察中均显示出更优的脂质层修复效果.对于隐形眼镜配戴者, 仿脂质泪液补充剂不仅能显著缓解主观症状,提高患者满意度, 还能改善眼睑刷上皮病变和角膜染色等临床体征[45].

一项针对231名蒸发过强型干眼病患者的IV期多中心随机双盲研究[101]显示:两种含脂质滴眼液(每日4次, 疗程35天)在延长 TBUT 方面效果相当, 且耐受性良好.大型临床试验证实, 含 HP-guar 的磷脂纳米乳剂可显著提升 TBUT, 并在长达8小时内持续缓解各类干眼病亚型(水液缺乏型,蒸发过强型及混合型)症状, 同时增加脂质层厚度 (LLT) 和眼部舒适度[102–104].

临床前研究表明, 含脂质补充剂具有更优的保湿性,眼表滞留能力和更快的修复效果, 可增强润滑作用并提升泪膜稳定性[105].临床试验证实, 其能显著延长BUT, 减轻包括灼烧感,砂砾感和刺痛感在内的干眼症状[104].含 HP-guar 的磷脂纳米乳剂可有效针对干眼病的关键病理环节, 既能快速缓解症状, 又能持续发挥作用, 同时改善眼表健康并提升泪膜质量[102]. 表 1 列出了多种市售含脂质滴眼液的成分组成及相关同行评议研究数据.

全氟己基辛烷滴眼液. 全氟己基辛烷滴眼液(商品名Miebo®, 美国Bausch＋Lomb 公司)是一种成分单一,不含水分且不含防腐剂的新型滴眼液制剂.其活性成分全氟己基辛烷具有两亲性, 由疏脂性氟碳链段和亲脂性烃链段组成[48].该制剂于 2023 年获得美国市场批准, 此前已在欧洲,澳大利亚和新西兰上市多年(商品名EvoTears®/NovaTears®), 包括添加或不添加ω-3脂肪酸的剂型[132,133].尽管该类别中大多数泪液补充剂无需处方即可购买, 但由于其活性成分未列入药品标准专论, 该泪膜稳定剂在某些国家需凭处方使用.

全氟己基辛烷治疗干眼病的体征和症状的作用机制已有多种假设.其一是通过在泪膜与外界环境的界面形成单分子层, 抑制泪液蒸发[48,134,135].体外研究表明, 全氟己基辛烷滴眼液在减少生理盐水蒸发方面优于泪液补充剂和从健康志愿者提取的睑酯[47], 但这一结果尚未通过临床设备在体内得到证实.在健康家兔的临床前实验中, 局部使用全氟己基辛烷单次给药 5 分钟后即可改善脂质层分级, 连续给药5至 7 天后该效果仍得以维持.然而, 该健康动物模型中的泪膜蒸发率,泪液量和渗透压未见显著变化[136].与用于干眼病患者的阳离子纳米乳剂相比, 纳米乳剂使用后即刻增加泪膜脂质层厚度(LLT)并引发高阶像差, 而全氟己基辛烷则在12周内逐渐提升LLT, 且未引起高阶像差变化[137].一项针对干眼病合并 MGD 患者的4周研究也观察到脂质层分级和泪膜厚度的改善[138].局部使用全氟己基辛烷可降低角膜表面温度, 激活角膜瞬时受体电位阳离子通道亚家族M成员 8(TRPM8) 冷感受器, 这种反应可能增强反射性泪液分泌和瞬目, 缓解干眼症状, 减轻不适和疼痛[139].

多项临床研究已证实全氟己基辛烷治疗干眼病的有效性和安全性[140–144].一项II期研究显示, 每日2次或4次给予全氟己基辛烷均较等渗盐水对照组显著改善角膜荧光素染色总分和眼干症状, 其中每日4次给药方案疗效更显著[140].两项III期研究进一步证实, 每日4次给药组在首个评估时间点第15天和观察终点第57天时, 干眼病体征和症状的改善均显著优于低渗盐水对照组[141,142].

综合研究显示, 全氟己基辛烷最常见的不良反应为短暂性轻度视力模糊(发生率2.1%)[145].在中国患者中开展的III期研究也报告了相似结果[144]. RCT 研究表明, 接受该药物治疗的患者中视力模糊发生率为2.5% [50].基于严格的非临床研究, 局部使用全氟己基辛烷被证实是无毒且无生物累积性的[146].

一项III期多中心,单臂,开放标签研究对208名蒸发过强型干眼病患者进行评估发现, 每日4次使用全氟己基辛烷滴眼液治疗52周能显著改善干眼病体征和症状, 且患者耐受性良好[143].其中从生理盐水治疗转为全氟己基辛烷治疗的患者组(n=111)在转换治疗首个评估时

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表 **1.** 含脂质补充剂的相关研究示例

脂质成分	商品名(生产商)	已发表研究
蓖麻油	Optive Plus (美国Allergan公司)	Kaercher 等2014年[106]; Karcenty 等2021年[107]
	Refresh Endura (美国Allergan公司)	Di Pascual é等2004年[108]; Fogagnolo 等 2016 年[109]
	Refresh Optive Advanced (美国 Allergan 公司)	Jerkins 等2020年[101]
中链甘油三酯	Liposic (美国Bausch + Lomb 公司)	Wang 等2010年[110]; Chung 等2016年[111]; Kim 等2017年[112]
	Artelac Lipid (美国 Bausch + Lomb 公司)	Mihaliz 等2018年[113]; Lim 等 2020 年[114]
矿物油	Cationorm (日本 Santen 公司)	Robert 等2016年[115]; Lim 等2020年[114]; Fogagnolo 等 2020 年[116]; Makri 等2021年[117]
	Retaine (美国境外称 Cationorm)	Ousler 等 2015 年[118]
	Soothe (美国Bausch + Lomb 公司)	Fogagnolo 等 2016 年[109]
	Soothe XP (美国 Bausch + Lomb 公司)	Korb 等 2005 年[119]
矿物油+磷脂	Systane Balance (美国Alcon公司)	Aguilar 等2014年[120]; Guthrie 等 2015 年[45];Gokul等2018年[121]; Jerkins 等2020年[101]
	Systane Complete (美国 Alcon 公司)	Silverstein 等2020年[102]; Yeu 等 2020 年[103]; Muntz 等2020年[46]; Pucker 等2021年[122]; Craig 等2021年[98]; Antman 等2024年[123]
ω-3 脂肪酸(亚麻籽油)	Refresh Optive Mega-3 (美国 Allergan 公司)	Deinema 等 2017 年[124]; Fogt 等 2019 年[125]; Downie 等 2020 年[126]
脂质体喷雾	Tears Again (德国 Optima 公司)	Turnbull 等2018年[117]
磷脂	Emustil (意大利 SIFI 公司)	McCann 等 2012 年[128]
	Tears Again (瑞士 Optima Medical 公司)	Craig 等 2010 年[129]; Rohit 等 2017 年[130];Essa等2018年[99];Pult等 2021 年[131]

间点4周时即出现症状和体征的明显改善[143].另一项多中心单臂研究显示, 单次给药后5分钟和60分钟即可观察到干眼症状缓解, 每日4次给药方案在治疗第3天,7天和14天也持续显示疗效[49].

2023年发表的一项系统综述分析了6项 RCT 研究, 结果显示与对照组相比, 使用全氟己基辛烷滴眼液的患者在多数观测指标(OSDI,LLT,角膜染色及不良事件发生率)上均表现出更明显的改善[133], 但对照组的 TBUT 相对更长[133].最新一项 Meta 分析表明全氟己基辛烷是治疗继发于 MGD 的蒸发过强型干眼病安全有效的替代疗法, 能显著改善角膜染色和眼干症状[50].

含海藻糖的泪液补充剂. 海藻糖是一种天然二糖, 由两个葡萄糖分子组成, 具有稳定蛋白质和细胞膜结构,防止变性及抑制氧化损伤的作用[147–149].体外实验表明, 当海藻糖与透明质酸滴眼液联用时, 海藻糖能增强自噬通量[150], 这种作用有助于发挥渗透保护效应, 并维持干眼病中上皮细胞的稳态[150].这一机制十分关键, 因为自噬作用可通过降解和回收细胞组分, 使细胞适应干燥状态.在干眼病干燥模型中, 一种含3%海藻糖与0.15%HA的无防腐剂配方(Thealoz® Duo;法国Thea公司)与含0.001%氢化可的松和0.2%HA的组合相比, 可显著促进杯状细胞恢复并减少炎症标志物表达[151].

临床研究表明, 含海藻糖的泪液补充剂具有优异的安全性 [152].一项纳入 10 项 RCT 的系统综述探讨了其在干眼病中的应用[153].与对照组相比, 含海藻糖的泪液补充剂可显著改善眼部舒适度及稳态指标(TBUT和角膜染色), 且所有纳入研究均未报告不良事件[153].自该系统综述发表后, 多项新研究进一步比较了海藻糖(多与透明质酸联用)与其他配方的疗效.研究证实该配方对干眼病患者[154],围绝经期及绝经后女性[155],以及白内障术后患者[156]均具有显著治疗效果.

含依克多因的泪液补充剂. 依克多因(Ectoine)是一种源自细菌的极端微生物保护剂, 能够保护蛋白质和生物膜免受极端环境条件的损害, 被视为天然渗透保护剂[157].一项纳入18名干眼病患者的前瞻性研究显示, 使用不含防腐剂的依克多因眼部喷雾剂, 每日3次, 持续约2周, 可减轻干眼症状并延长 TBUT [158].在一项干燥小鼠模型研究中, 对比局部使用依克多因滴眼液与赋形剂对照组, 发现依克多因以浓度依赖方式保护小鼠角膜免受损伤, 1.0% 和 2.0% 浓度的依克多因可显著恢复角膜规则性并减少角膜染色.暴露于干燥环境的小鼠角膜和结膜中, 多种促炎细胞因子和趋化因子表达显著升高, 而1.0%和2.0%依克多因可将这些炎症介质抑制至接近正常水平[159].在另一小鼠研究中发现局部使用2%依克多因通过恢复IL-13/γ-干扰素信号通路的平衡, 显著减轻角膜损伤, 同时提高杯状细胞密度和黏蛋白分泌量[160].

含抗氧化剂的泪液补充剂. 含有抗氧化剂的口服营养补充剂常被推荐用于改善眼部健康, 尤其是年龄相关性黄斑变性[161].尽管抗氧化剂作为泪液补充剂成分在白内障领域已被研究[161], 但其在干眼病患者中的应用仍缺乏充分数据支撑.

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抗氧化剂主要存在于亲脂性膜和脂蛋白(如维生素E和泛醇)或水相成分(如抗坏血酸,谷胱甘肽和硫氧还蛋白)中[162].

一项针对糖尿病合并干眼病患者的研究显示, 局部联合应用α-硫辛酸(一种天然存在的可同时作用于脂质和水相的双相抗氧化剂)与羟丙基甲基纤维素, 在改善角膜染色方面优于单独使用羟丙基甲基纤维素, 两组患者的TBUT均有改善[162].

硒在细胞中的应用可增加硒蛋白的表达, 通过上调抗氧化酶的表达来抵消活性氧(ROS)的作用[163].

含维生素的泪液补充剂(A;B12;C;D). 在干眼病相关研究中, 维生素通常作为口服补充剂而非局部应用的泪液补充剂成分.具体信息参见 12.2 节.

维生素A, 尤其是作为口服补充剂, 可能是干眼病领域研究最广泛的维生素[16].维生素A作为局部补充剂的效果也已被研究.一项 RCT 研究在150名干眼病患者中对比了局部使用维生素A(棕榈酸视黄酯, 0.05%, 每日4次),环孢素A(CsA, 0.05%, 每日2次)及对照组的疗效[164].结果显示, 两个治疗组包括TBUT,角膜染色,杯状细胞密度及印迹细胞学分级在内的症状和体征均得到改善[164].但最新综述指出[11], 维生素A代谢产物异维A酸(13-顺式维甲酸)会损害睑板腺健康[165,166].该物质能抑制人类睑板腺上皮细胞增殖并促进其死亡[165,166], 这可能是其诱发 MGD 的重要机制[166,167].

据报道, 维生素 B12 具有抗氧化和抗炎特性, 因此在30 名患有干眼病的绝经后女性中, 对含0.3% HA的局部药物的效果进行了评估[168].与基线相比, 0.3% HA 和维生素 B12 滴眼液减轻了干眼症状, 并改善了泪膜稳定性和泪液量, 但仍需更大规模的 RCT 研究来确定该组合是否优于单独使用 HA .另一项针对中重度干眼病患者的研究也发现, 含0.15%HA,0.5%PEG 8000和维生素B12的制剂也具有类似的症状和体征改善效果[169].

抗坏血酸是一种天然的维生素 C, 作为一种抗氧化剂, 已知其通过清除ROS来维持自由基平衡[170].一项研究报道了使用含有抗坏血酸和间充质干细胞来源外泌体的滴眼液, 在体外和体内均显示出减少眼表炎症和减轻眼表损伤的效果[171].

一项系统综述和 Meta 分析显示, 干眼病患者的血清维生素D水平显著降低, 且与 OSDI 评分呈相关性, 但与其他干眼病参数无显著关联[172].目前关于维生素D直接加入局部润滑剂的研究极为有限.在一项研究中, 8名阻塞性 MGD 患者接受维生素D3类似物的眼睑局部治疗[173].经过8周治疗后, 这些患者在睑板腺开口堵塞,睑缘血管化, TBUT,睑酯质量及睑板腺面积等临床指标上均较治疗前显著改善.此外, 口服维生素D补充剂通过减轻眼表损伤和降低泪液中炎症标志物水平, 能显著改善泪液分泌量,稳定性和质量[172,174–176].

总之, 现有证据表明抗氧化剂和维生素可能在干眼病治疗中具有一定作用.然而, 在将其广泛应用于临床治疗前, 仍需通过高质量研究进一步验证其单独使用或与其他成分联用时的安全性和有效性.

使用泪液补充剂面临的挑战. 患者在选择泪液补充剂时往往需要反复尝试, 这不仅带来高昂的经济负担, 还容易产生挫败感[177].一项纳入了43项RCT, 3497名干眼病患者的Cochrane系统综述[178]显示, 虽然泪液补充剂能有效缓解症状, 但由于缺乏高质量的比较研究, 目前仍无法确定哪种产品最有效.此外, 各研究在诊断标准,实验设计和测量指标方面也存在较大差异[178].该综述还得出0.2%聚丙烯酸的泪液补充剂在缓解干眼症状方面优于1.4%聚乙烯醇的产品[178], 但由于不同研究结果存在矛盾, 无法对其他类型的泪液补充剂得出明确结论.

近期一项系统综述指出, 复方制剂比单成分活性药物更有效[94].其中, CMC 与HA的组合疗效优于单独使用任一成分;HA(尤其是低分子量透明质酸钠)与添加海藻糖联用可增强疗效; CMC 中加入甘油也能提升作用.此外, 基于PEG的润滑剂被证实比 CMC+ 羧甲基纤维素钠或羟丙基甲基纤维素产品更有效[94].

一项近期平行对照研究[179]在每组20名中度干眼病患者中比较了五种不同润滑剂滴注后1小时内的效果(每15分钟评估一次), 并将未给药的对侧眼作为对照.这五种市售润滑剂分别基于含0.5%和1% CMC ,0.1% HA+trehalose,0.4% PEG 400+0.3% propylene glycol以及0.1% HA+0.4% PEG 400+0.3% propylene glycol的产品.在整个测试期间, 各产品组间及测试眼与对照眼相比, TMH和眼红在任何时间点均无差异.所有测试眼在各时间点的NIBUT均较对照眼显著增加, 但各产品间未显示优劣差异.这些结果表明不同配方的润滑剂均可快速实现泪膜稳定性的短期改善[179].

关于治疗剂量和疗程的观察效果仍存在争议.一项纳入64项 RCT 的系统综述得出, 每日4次使用润滑剂可在1个月内改善干眼症状[94].相比之下, 干眼病体征的改善约需4个月时间[98].这与给予患者的临床建议高度相关.若使用润滑剂至少1个月后症状未见改善, 患者应考虑更换人工泪液产品或采用替代治疗方案.约25%的患者可能对特定人工泪液无效[98].这一结论也对研究设计产生影响, 持续时间短于4个月的研究不太可能观察到眼表和泪膜参数的临床改善.

在使用泪液补充剂时需考虑一些实际问题.不同瓶型因其材质强度和滴注机制各异, 可能对手部灵活性或握力欠佳的患者造成使用困难.一项研究测试了60种不同瓶子(57种润滑剂和3种干眼病药物)所需的平均挤压力[180], 结果显示多剂量无防腐剂瓶型所需力度最大.这表明在选择干眼病治疗产品时应考虑患者手部功能, 因为滴瓶的易挤压性可能影响用药依从性.

润滑剂的储存也是一个考量因素:部分患者将润滑剂存放在冰箱中, 以在使用时获得清凉舒爽感.然而, 许多产品的复杂配方可能因冷藏受到不良影响, 黏度等因素可能改变, 导致使用时舒适度下降或影响视力.事实上, 研究已表明冷藏储存并无显著的舒适性优势[181,182].

综上, 对现有文献的分析表明, 尽管泪液补充剂种类繁多且大多可在药店直接购得, 但对于不同亚型干眼病的治疗, 何种配方更优尚未形成共识.然而证据显示, 脂质缺乏型患者从含脂质的补充剂中获益最多[98].每日 4 次,持续 1 个月的规范使用, 或可判断某类人工泪液是否能有效缓解症状;而若要观察对体征的改善, 则需持续使用约四个月[98].

当前研究正持续探索新型聚合物组合和先进递送系统, 以进一步提升泪液补充剂疗效.基于纳米技术的载体和可生物降解微球等创新技术正在研发中, 旨在实现润滑剂和治疗药物的缓释作用, 或将为慢性重度干眼病

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患者带来更大获益[96].未来研究需统一实验设计, 包括核心评价指标的选择, 并开展基于循证医学的高质量临床研究, 在明确界定的干眼病患者群体中, 通过足够长的随访期对不同产品进行对比.

- 泪液保存装置:

接触镜

接触镜可能因影响眼表而成为干眼病的风险因素[183], 因此干眼病管理可能需要调整接触镜材料,设计,更换频率或护理系统以减轻这种影响[184,185].但另一方面, 接触镜也能保护眼表, 使其在润滑不足的情况下, 免受眼睑运动产生的应力影响, 减少角膜干燥, 从而可能通过屏蔽痛觉感受器来促进角膜愈合和减轻疼痛[186].

长期佩戴的亲水性绷带镜片材料可在一周内减轻白内障摘除及人工晶体植入术后合并 MGD 患者的干眼病体征和症状[187,188].一项针对干燥综合征患者的研究显示, 持续使用硅水凝胶绷带镜片(每三周更换一次)六周后, 其疗效优于三个月的自体血清治疗[189].软性接触镜还可用于固定眼表羊膜(详见第10.3节)[190], 也能用于优化眼表药物递送[191,192], 但尚未开发出用于干眼病管理的商业化产品.

过夜佩戴角膜绷带镜会增加感染性角膜炎的发生风险.[193–195], 而在严重干眼病佩戴者中这种风险会加剧[186,196].此类情况下, 通常会在治疗方案中添加无防腐剂的局部抗生素以降低严重感染的风险[186].

巩膜镜已被用于治疗干眼病患者[197], 其通过增强视觉功能和改善眼表健康的双重治疗作用发挥功能.一项对134名巩膜镜佩戴者的回顾性研究显示, 除两名受试者外, 所有患者从镜片适配到随访期间 OSDI 评分均有改善, 且与佩戴时长无关[198].这些镜片由刚性高透氧聚合物制成, 可跨越角膜并贴合于巩膜表面[186,199,200].该设计在镜片后表面与角膜上皮前表面之间形成一定空间, 可填充人工泪液或生理盐水, 持续提供湿润环境并防止眼表蒸发.据报道, 该镜片对严重干眼病患者具有良好疗效和耐受性[201].在一项关于巩膜镜联合富生长因子血浆(PRGF)滴眼液治疗各类眼表疾病患者的回顾性报告中, 该联合疗法被证实能安全有效地缓解患者症状[202].镜片的刚性特质还可防护眼睑运动造成的角膜微损伤, 同时减少泪膜蒸发, 其增加的泪液量带来显著临床获益.由于巩膜镜能矫正此类患者常存在的不规则散光, 可用于改善视力[186].

多项研究报道, 对于患有 Stevens-Johnson 综合征,干燥综合征及眼移植物抗宿主病等各种潜在疾病的干眼病患者, 巩膜镜均能改善其视力[203–206].巩膜镜的使用还可改善角膜和结膜的染色评分, 并降低泪液渗透压水平[203,205,207].患者干眼症状得到改善(以 OSDI 评分改善为表现)的同时, 生活质量评分也得到提高[203,205].巩膜镜的液体储留区已被用作药物递送的一种方式.一项研究报道, 在液体储留区中加入贝伐珠单抗可改善角膜新生血管和视力[208], 另一项研究则在 9 名干眼病患者的液体储留区中装载了CsA [209].

要充分发挥巩膜镜的治疗效益, 必须确保镜片配适参数最优化[200,210].这对于同时伴有眼表损害的干眼病患者尤为重要.通过实现良好的边缘对齐,中央及角膜缘穹隆匹配, 同时避免中周部血管压迫, 可显著提升佩戴舒适度.巩膜接触镜使用中常见的挑战是日间雾视现象, 这是由于液体储留区内碎屑积聚所致[186,200,211,212].镜片湿润性不足也可能导致不适感加重并影响视觉功能.尽管如此, 巩膜镜的使用通常不会引发严重并发症, 且能有效改善干眼病的症状和体征[200,205,207,213,214].然而, 尽管该疗法在临床实践中相对常用, 目前仍缺乏强有力的研究证据支持巩膜镜用于干眼病患者的标准化管理.

湿房镜

湿房镜可围住眼睛周围区域, 从而限制眼周气流,增加眼周湿度并降低泪膜蒸发速率 [32,33,215].海绵衬垫可进一步提高眼周环境湿度.为确保其有效性, 镜框需根据患者面部形状调整, 以最大程度减少漏气.

一项针对 30 名干眼病患者评估湿房镜短期效果的研究显示, 眼舒适度, TMH ,NIBUT 和 LLT 随时间持续改善, 在 60 分钟时达到峰值后逐渐下降, 但与接受无菌生理盐水滴眼的对照组相比, 这些数值仍高于基线水平[33].另一项纳入14 名干眼病患者的研究表明, 当暴露于可控风环境10分钟后, 佩戴湿房镜者比佩戴传统眼镜或不戴眼镜者具有更好的眼舒适度, 其泪液蒸发率和眨眼频率也更低, 且暴露后的眼表指标(TBUT 和荧光素染色)与基线无明显差异[31].

泪点栓塞

泪点栓塞被公认为中重度水液缺乏型干眼病的治疗手段[2], 其通过部分或完全阻断泪液引流系统来增加眼表液体潴留.一项包含18项胶原蛋白或硅胶泪点栓的 RCT 研究的Cochrane系统综述显示, 该治疗对干眼症状或体征的改善并无确定性结论[216].其中一项试验发现, 植入泪点栓的患者的人工泪液使用频率低于未植入者.但由于所采用泪点栓类型,干眼病亚型及患者严重程度的差异, 以及缺乏标准化试验方法, 现有证据尚不足以明确其疗效与安全性[216].该综述还指出, 泪点栓塞可能导致并发症, 包括泪溢,栓子移位, 极少数患者可引发炎症和感染性并发症, 如泪小管炎,化脓性肉芽肿及泪囊炎[216].

在一项前瞻性,纵向,单中心研究中, 30名中度干眼病患者的下泪点被植入不可吸收性泪点栓, 术后3周发现, 包括谷胱甘肽合成酶和IL-1在内的泪液蛋白表达上调, 而胆碱能受体(神经元)α-7和淋巴细胞胞浆蛋白-1表达下调[217].

一项纳入 50 例干眼病患者的 RCT 研究中, 患者分别接受泪小管内注射羟丁基壳聚糖溶液(其胜生物科技有限公司, 中国上海)或 VisiPlug® 治疗(Lacrimedics Inc, 美国), 结果显示治疗 12 周后, 两种方法均较基线显著缓解 干眼症状和体征[218].

一项研究调查了因不适感(主要由于泪点塞突出, 伴有或不伴有肉芽形成)而从干眼病患者中取出硅胶泪点塞后的微生物学结果[219], 其细菌培养阳性率为42.2%, 其中克雷伯菌属最为常见(18.5%).药敏试验结果显示对万古霉素的敏感率为100%, 第三代头孢菌素为88.5%, 在测试的喹诺酮类药物中对左氧氟沙星的敏感率为81.0%[219].这些发现结合本地区眼表分离菌株的耐药谱特征, 可为硅胶泪点栓相关并发症的抗生素选择提供指导[220,221].

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新型泪点栓设计及其他技术

一项单中心,前瞻性,开放标签试验研究评估了一种由交联HA制成的泪小管栓.该研究纳入了63例人工泪液治疗无效的干眼病患者.结果显示,在佩戴3个月后,患者的角膜染色评分,Schirmer 试验值,TBUT 和 TMH 均较基线水平显著改善[78].

一项前瞻性,多中心,双盲 RCT 对157例受试者进行了研究,比较新型交联HA泪小管填充剂(LACRIFILL® Canalicular Gel;Nordic Pharma,荷兰)与市售水凝胶泪小管栓的疗效[222].研究将填充剂或泪小管栓植入下泪小管后,发现填充剂在 Schirmer 评分和 OSDI 评分方面的效果均不低于泪小管栓.该研究结论认为,交联HA填充剂通过泪小管阻塞治疗干眼病具有安全性,耐受性和有效性,其对干眼病体征和症状的临床及统计学显著改善效果可持续6个月[222].

其他创新技术也正在探索以提高泪点栓治疗干眼病的疗效.载药水凝胶或有机凝胶的泪点栓采用高生物相容性HA衍生物或CsA等免疫调节剂,已在体外和体内实验中进行了测试[223,224].虽然3D打印技术已被用于制造具有内置给药系统的个性化泪点栓,可根据个体泪点形态进行定制,但迄今尚未见相关临床研究发表[225].

- 泪液修复或泪液分泌刺激治疗:由于泪液量减少或成分改变导致的泪液缺乏可引发干眼病.针对泪膜中特定成分的缺失,可通过不同方法(详见第6.3.1,6.3.2和6.3.3节)来修复或刺激相应泪膜成分的生成.如第6.3.4节所述,新兴的"神经调节"疗法通过增强三叉神经活性来刺激包含多种泪液成分的泪液分泌.

脂质层的修复与分泌刺激

2011年 TFOS 关于 MGD 的专家共识表明,MGD 是干眼病发生发展的重要驱动因素[167,226–229],这促使大量研究致力于优化其管理,增强脂质向眼表的递送.

睑板腺功能障碍:家庭治疗. 热敷疗法

热敷疗法被用于治疗 MGD,其目的是融化腺体内增稠的睑酯,便于后续通过人工按摩促进腺体排出.热敷旨在增加泪膜LLT并改善腺体功能.

近年来,患者可自行操作的居家疗法选择激增,包括非处方热敷产品(从加热湿毛巾,市售热敷产品到更具技术性的电子设备)[230–243].消费者可通过电商平台和小型制造商便捷获得这些居家治疗产品.然而,并非所有可用产品都具备安全性和有效性证据,甚至缺乏标准化的使用方法[234,236,241].

阻塞的睑板腺分泌物熔点高于正常腺体[244].因此,建议使用40°C至41.5°C的加热温度,并确保足够的作用时间以达到治疗效果[245],使用时需注意温度不宜过高,以免烫伤皮肤或对眼睑及眼表造成其他不良反应[236].

热敷疗法可根据热源性质分为干热型和湿热型,进一步细分为化学加热型,微波加热型和电子加热型.需注意的是,不同类型的热敷可能具有不同的疗效[234,239].一项研究比较了干热和湿热敷贴的效果,发现湿热治疗过程中眼睑可能变得潮湿,由于蒸发冷却效应反而可能产生不利影响[246].现有的有限证据表明,建议每日至少使用一次加热设备(每次10分钟)[239]或每日两次(每次5分钟)[247],随后配合轻柔的眼睑按摩以帮助排出睑酯.研究发现,每两分钟加热至45°C的毛巾与市售热敷设备具有相似的热传导效果[241],但该方法耗时较长,长期使用可能影响患者依从性.

热敷后需要进行眼睑按摩以排出睑酯并帮助疏通阻塞的睑板腺[241,248–250].虽然长期的眼睑和眼球按摩被认为与角膜变形和圆锥角膜有关,但一项前瞻性研究评估30分钟眼睑热敷和按摩后角膜地形图的变化,发现其在观察期间无显著差异[251].

多项新产品的疗效已被报道,但支持证据的确定性程度各不相同[230,232,233,235,238,252–255].临床医生在指导患者了解这些产品的支持证据并推荐适合其具体诊断的治疗方案方面发挥着越来越重要的作用.

一项研究通过检测20名健康受试者和35名干眼病患者泪膜的变化,评估了含有薄荷醇的热敷作为干眼病潜在治疗方法的效果[256].重复使用含薄荷醇的热敷显著增加了两组受试者的泪河体积和 TBUT.作者认为这种热敷刺激了TRPM8通道,可能成为干眼病的一种潜在新型治疗方法[256].

先前已有关于使用热敷治疗 MGD 的临床研究综述发表[230,234,236,241]. 表 2 汇总了采用不同热敷方法的多项研究及其主要发现.

目前仍有多个关键问题需要进一步研究和明确,包括:

市场上多数热敷眼罩普遍缺乏临床研究数据;

热敷时长缺乏循证依据;

热敷后眼睑按摩的方式及时长缺乏标准化方案;

长期佩戴 "重型" 眼罩(如患者佩戴时睡着)对角膜地形图的影响尚不明确.

必需脂肪酸

多不饱和脂肪酸 (PUFA),如ω-3,可改善 MGD 患者的干眼病体征和症状[258–263],但部分研究未能证实口服ω-3对 MGD 指标有积极影响[264,265].

一项前瞻性,随机,双盲对照试验纳入50例伴有 MGD 体征的轻中度干眼病患者[262].患者被分为两组:ω-3 组 24 人,安慰剂组 26 人.ω-3 组摄入 600 毫克二十碳五烯酸 (EPA) 和 1640 毫克二十二碳六烯酸 (DHA),安慰剂组摄入 3000 毫克橄榄油.治疗4周和8周后,两组 TBUT,角膜染色及 OSDI 评分均显著改善.治疗8周后,ω-3组的 TBUT 和 MGD 评分改善程度显著优于安慰剂组[262].

另一项多中心,研究者盲法的随机研究在107例白内障术后 MGD 患者中评估了再酯化甘油三酯型ω-3的疗效[263].患者被随机分成ω-3 组和对照组.经12周治疗后,ω-3组的 TBUT,角膜染色,SPEED 问卷和 OSDI 评分较对照组显著改善.此外,仅ω-3组中重度 MGD 患者的睑板腺质量与排出能力显著提升[263].

局部药物治疗

TFOS 睑板腺功能障碍专家共识指出,腺体阻塞的核心机制是导管过度角化和睑酯黏性增加,进而导致开口栓塞,导管阻塞扩张,最终临床表现为腺体萎缩[167].

局部应用阿奇霉素

局部应用阿奇霉素也是治疗 MGD 的选择之一,其疗效与口服多西环素等抗生素相当,且无全身性副作用(最常见为胃肠道不适)[266–268].未来需要更大样本量,覆盖不同人群的 RCT 来评估阿奇霉素等局部抗生素长期治疗 MGD 的效果.

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表 2. 热敷治疗 MGD 的研究示例

研究(年份)	受试者类型	治疗方法	产品对照	样本量	持续时间	随机化	改善的结果指标	与对照无显著差异的指标
Leeungurasatien 等, 2020 [238]	健康人群	小麦热敷包	陶土热敷包	30(交叉设计)	10 分钟使用, 10 分钟后评估	是	-	眼睑表面温度,组织血流
Travé-Huarte 和 Wolffsohn, 2021 [243]	干眼病(TFOS DEWS II 标准)	水动力加热眼部按摩仪	无治疗	15	2 周	是	症状	渗透压,NIBUT, TMH ,LLT,角膜和结膜染色,心率,睡眠模式
Garcia-Marques 等, 2022 [235]	干眼病(TFOS DEWS II 标准)	18~31 岁人群使用 MGDRx 眼罩	61~90 岁人群使用 MGDRx 眼罩	30 名年轻人; 30 名老年人	2 周	否	NIBUT ,LLT	症状,睑板腺缺失,睑酯质量,腺体阻塞
Arazi 等, 2024 [254]	睑板腺疾病	眼镜佩戴式红外加热装置	无	10	2 周	否	-	症状, TBUT , Schirmer 值
Wang 等, 2024 [257]	混合型干眼病	一次性自热眼罩	热棉毛巾	134	12 周	是(非盲法)	症状, TBUT ,角膜染色	Schirmer 值

LLT: 脂质层厚度; NIKBUT: 非侵入性泪膜破裂时间; OSDI: 眼表疾病指数; TBUT: 泪膜破裂时间; TMH: 泪河高度

局部应用硫化硒

硫化硒局部制剂是治疗角化过度性疾病,花斑癣,脂溢性角化病和其他皮肤病的有效药物[269,270].硫化硒可分解蛋白质聚集体, 并可能减缓角蛋白的进一步沉积[271].硫化硒产品难以穿透上皮屏障, 必须直接作用于目标部位, 通过氧化还原反应破坏二硫键, 从而使蛋白质解聚[272–274].含硫化硒的AZR-MD-001(Azura Ophthalmics公司, 以色列)是一种眼科使用的半固体软膏.一项II期研究纳入245名 MGD 患者, 每周两次在睑缘涂抹该软膏, 三个月后患者症状(通过 OSDI ,视觉模拟量表和 SPEED 问卷评估)和临床体征均有所改善[271].与对照组相比, 治疗三个月后能分泌液态睑酯的腺体数量,睑酯质量和TBUT均有所改善, 且这种改善持续至治疗后六个月[275].另外两项研究分别针对67名 MGD 患者和接触镜不耐受的患者, 结果显示其能分泌液态睑酯的腺体数量,睑酯质量, TBUT 和接触镜佩戴时间均有改善[276,277].这些研究表明, AZR-MD-001每周仅需睡前使用两次, 即可安全,有效且耐受性良好地治疗继发于 MGD 的蒸发过强型干眼病.

睑板腺功能障碍:门诊治疗. 设备驱动技术:眼睑内侧加热与按摩

LipiFlow® 热脉动系统(强生公司, 美国)是一种临床使用的矢量式热机械疗法, 通过单次治疗向睑板腺施加局部热量和压力, 促进睑酯流动以补充眼表泪膜脂质层[2].该治疗需提前进行表面麻醉.研究表明, 单次治疗即可增加睑板腺分泌并缓解干眼症状, 且效果可持续至少六个月[278,279].一项针对20例继发于 MGD 的蒸发过强型干眼病患者的研究显示, 单次12分钟的热脉动治疗可显著改善睑板腺分泌和 SPEED 评分, 且效果持续长达三年[280].

一项文献综述评估了11篇关于LipiFlow治疗干眼病的疗效的文章[281].虽然LipiFlow相较于热敷治疗显示出一定优势, 但是, 三项没有受到产业界资助的研究得出结论:当热敷和眼睑清洁方案执行得当时, LipiFlow的疗效并未显著优于这些传统方案[281].另一项系统综述对13项试验共1155名受试者的结果进行分析[282], 未发现LipiFlow与热敷在睑板腺分泌情况,睑酯质量或TBUT方面有显著差异.另有五项研究显示, 恒温设备(TearCare,iLux,MiBoFlo)在治疗4周时 OSDI 评分平均比LipiFlow低4.59分, 不过该证据的确定性较低[282].比较LipiFlow联合睑缘清洁与单纯睑缘清洁时, 在任何评估时间点均未发现体征或症状改善的证据[282].

Systane iLux®(TearFilm Innovations公司, 美国)是一种眼睑热脉动系统, 由一次性患者接触设备和手持式电池供电仪器组成[283,284].该系统通过维持38~42°C的眼睑温度来融化睑酯, 同时压迫和排出睑板腺分泌物[283,284].治疗前同样需要进行表面麻醉.两项临床研究均无与设备使用相关的不良事件被报告[283,284].

Systane iLux与LipiFlow治疗相比, 两种方法在治疗4周后均能改善 MGD 的体征和症状(包括睑板腺评分, TBUT 和 OSDI 评分), 且结果无统计学差异[283].另一项随机试验表明, 单次iLux治疗12个月后, 仍能改善临床指标(如睑板腺评分,NIBUT)和患者症状(干眼病对日常生活影响-症状困扰量表)[285].

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一项关于多种临床热疗法的综述指出，对于偏好单次治疗而非持续6-12个月的治疗或难以依从家庭治疗时间强度的患者，iLux可能是更好的选择[284].然而，虽然这类临床治疗能快速缓解症状且效果可能持续长达一年，但其费用远高于家庭治疗方案[284].新一代设备iLux2®已上市，该设备用显示屏取代了放大镜，可用于睑板腺成像，因此兼具诊断和治疗的功能.

设备驱动技术:眼睑外部加热

TearCare®系统(Sight Sciences公司，美国)包含四个电热装置(SmartLids®)，通过粘合方式固定在上下眼睑[284,286–288].这些装置在单次治疗中以41°C至45°C温度范围内提供15分钟的可控热能治疗[288].眼睑加热后，由眼科护理人员手动进行睑板腺按摩[284,286–288].由于该装置置于眼睑外部，无需麻醉，患者在治疗期间可正常眨眼并进行日常活动(如阅读,看电视等).

与每日热敷方案(每组n=12)相比，TearCare治疗改善了TBUT (两周内提升近12秒),显著改善角膜和结膜染色评分以及睑板腺评分，效果持续超过六个月[287]，且无不良事件被报告.治疗组在第七个月接受再次治疗后，客观指标和主观症状均获得进一步改善[287].

一项多中心RCT研究对MGD所致干眼病患者进行了分析，受试者在基线时接受单次TearCare治疗(n=67)或单次LipiFlow治疗(n=68)，在治疗后随访一个月，发现两组在TBUT,睑板腺分泌评分和症状方面均显著改善，且两种治疗方法在所有结果上均无显著差异[289].研究结果表明，单次TearCare治疗能显著缓解MGD患者的干眼病体征和症状，其安全性和有效性与单次LipiFlow治疗相当[289].在后续的一项多中心RCT中，MGD患者接受单次TearCare治疗(n=115)或单次LipiFlow治疗(n=120)，治疗后随访1个月的数据显示，基于OSDI和SANDE的评估结果，对于更严重的MGD患者，TearCare在改善视觉质量和总体干眼症状频率方面显著优于LipiFlow [290].

另一项研究显示，在6个月的治疗期内，接受TearCare治疗的患者在TBUT和睑板腺评分方面的改善显著优于每日2次使用CsA滴眼液(Restasis®，艾伯维，美国)的患者[291].两组患者的症状改善程度相似，结膜和角膜染色评分,睑板腺评分以及Schirmer试验结果也基本相当[291].

MiBoFlo Thermoflo®(MiBo Medical公司，美国)是一种恒温治疗设备，采用镀银手持探头在无需表面麻醉的情况下向外部眼睑传递热电能量，将温度维持在42°C达10分钟[292].一项包含102名MGD患者的回顾性病例系列研究显示，在接受三次MiBoFlo治疗(每次间隔两周)后，随访6个月时患者的SPEED问卷评分较基线改善36%，OSDI问卷评分改善35%[293].角膜和结膜染色评分，TBUT,渗透压以及能分泌液体的腺体数量均显著改善，且无与设备相关的不良事件被报告[293].

在一项纳入54名MGD患者的前瞻性临床试验中，MiBoFlo和LipiFlow治疗均能改善OSDI评分和睑板腺分泌功能，但对NIBUT,角膜荧光素染色及睑板腺缺失情况无显著影响[292].另一项非随机病例系列研究显示，患者分别接受MiBoFlo联合手动按摩或LipiFlow自动治疗[294].在6个月随访时，两种治疗均能改善OSDI和SPEED问卷评分,角膜染色,丽丝胺绿结膜染色及TBUT.其中，MiBoFlo联合手动按摩治疗组在主观和客观评分改善程度均优于LipiFlow治疗组.

采用潜热原理的护目镜式治疗设备(商品名:Blephasteam®，法国)此前已在TFOS DEWS II治疗报告[2]和其他研究中描述[295,296].一项纳入73名受试者的前瞻性研究中，该设备每日使用两次，持续21天后[297]，受试者反馈治疗过程舒适，且治疗期间可进行日常活动(如看电视,阅读和使用电脑)，且无不良事件被报告.受试者症状评分(视觉模拟量表评估)显著降低，但Schirmer值,渗透压及TBUT在研究期间未见显著变化.

一项为期三个月的RCT研究将MGD患者分为三组(热毛巾组,EyeGiene®自加热眼罩组及Blephasteam组)[298].与热毛巾组相比，Blephasteam组症状改善显著，而EyeGiene®组与热毛巾组无显著差异.三组间Schirmer值,TBUT及睑板腺阻塞数量均未观察到显著变化.

另一项研究根据MGD严重程度评估了三种治疗方式(Blephasteam,脂质体喷雾剂和微波加热眼罩)的疗效[127]. NIBUT和脂质层分级在治疗10分钟后均获改善，且与治疗类型无关.其中，重度MGD组的NIBUT改善具有统计学意义，而轻症组和对照组的变化程度未达统计学差异.针对不同腺体缺失严重程度患者，仍需更多研究评估各类眼睑加热设备的疗效.

一项前瞻性病例对照研究采用红外热成像技术比较了热敷,Blephasteam及85°C左右桑拿10分钟对眼睑温度的影响[253].结果显示，Blephasteam能显著提升眼睑平均温度(较基线)，且效果优于传统热敷.

一项开放标签,随机研究评估了微波加热眼罩(TheraPearl，博士伦公司，美国)和Blephasteam在挪威轻中度MGD患者中的疗效[299].每日使用六个月后，两种治疗均改善了TBUT和OSDI评分，但两者效果无差异.值得注意的是，通过治疗日记发现，两种治疗方案的依从性在研究期间均有所下降，这仍是干眼病患者管理中的一个问题.

2021年的一项文献综述纳入了18篇关于湿热空气眼睑加热设备的研究[300].单次治疗结果显示:7项使用Blephasteam的研究和4项使用蒸汽原理研究原型设备的研究均观察到眼睑温度升高，以及LLT和TBUT的改善.

总体而言，采用潜热原理的Blephasteam设备能安全有效地将眼睑温度提升至治疗水平，并改善MGD患者的体征和症状，且耐受性良好.但目前仍缺乏比较该设备与其他眼睑加热设备在不同严重程度干眼病患者中疗效的RCT研究，同时关于湿热与干热疗法相对优势的证据仍显不足.

设备驱动技术:其他类型

IPL治疗

TFOS DEWS II治疗与管理报告指出，强脉冲光(IPL)是治疗MGD和干眼病的一种安全有效的方法[2].该技术已在皮肤科应用多年，用于改善多种皮肤问题，但其治疗干眼病的具体作用机制尚未完全明确.潜在的作用机制可能包括:封闭眼周皮下异常血管,加热睑板腺,激活成纤维细胞,减少睑缘细菌负荷,调节抗炎因子水平以及改变ROS水平等[301–304].

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IPL 治疗通过向眼周区域发射一系列非相干性多色光, 能够对受照射组织产生选择性光热解作用, 从而消融并减少睑缘的毛细血管扩张[305].

自2017年以来, 越来越多的临床试验评估了 IPL 治疗的有效性和安全性, 这些试验主要针对中重度 MGD 患者.研究表明 IPL 治疗能够减轻干眼病的症状和体征[306–309], 改善光学质量[308], 增强泪膜脂质层稳定性[309,310], 并减少对人工泪液的依赖[310].

一项纳入132名受试者的随机试验表明, 对于继发于 MGD 的干眼病治疗, IPL比每日使用传统热敷联合睑板腺按摩更有效[311].另一项纳入45名受试者的 RCT 研究将患者分为 IPL 联合睑板腺按摩组和单纯睑板腺按摩组[312].结果显示, 联合治疗在24周和32周时能改善睑缘异常,LLT, TBUT 和NIBUT,睑板腺评分及眼表荧光素染色评分, 并在32周时显著改善 SPEED 评分[312].另一项临床试验评估了三次 IPL 联合睑板腺按摩治疗与假治疗的效果, 发现在治疗1,3,6个月时能改善睑板腺分泌评分和 TBUT, 但在9个月时无显著差异[313].研究表明, IPL对睑板腺萎缩程度较轻[306],基线 TBUT 较低[314]以及较年轻的患者[315]效果更显著.

多项系统综述已总结了 IPL 治疗干眼病的现有证据.其中一项系统综述纳入了 IPL 治疗 MGD 有效性或安全性的3项 RCT 研究[316], 包含114名成人受试者(228只眼), 随访时间从45天至9个月不等.作者指出, 目前支持 IPL 治疗 MGD 有效性和安全性的 RCT 证据仍然缺乏, 且由于不良事件报告不完整, IPL的安全性仍不明确[316].另一项系统综述分析了2015至2021年间发表的11项 RCT 研究(759名受试者)[317], 作者报告 IPL 较基线可改善泪膜稳定性, 但对干眼症状的改善效果尚不明确.Lei等学者纳入了截至2022年1月的11项RCT(1842名受试者)[318], 其结果表明 IPL 治疗可显著降低 OSDI 和 SPEED 评分, 显著增加 TBUT 和NIBUT, 但对角膜荧光素染色无显著影响.最新系统综述包含截至2022年3月发表的13项研究(931名受试者)[319], 结果显示治疗后 TBUT 和 OSDI 评分显著改善, 但角膜荧光素染色和 SPEED 评分较基线无统计学差异.作者指出现有证据表明 IPL 可能作为干眼病患者的辅助治疗手段, 但需要通过更广泛的试验进一步验证该结论并阐明其作用机制[319].

IPL治疗通常作用于下眼睑下方皮肤及双侧颞部区域, 不包括上眼睑 [320].一项前瞻性试验中, 30名受试者接受标准 IPL 治疗, 其中半数被随机分配额外接受上眼睑 IPL 治疗[320].虽然两组干眼症状均有所改善, 但接受额外上眼睑治疗的受试者表现出更显著的改善, 且患者满意度依然很高[320].

在 IPL 治疗中, 可通过特定滤光片和能量密度调节光波穿透深度及发挥选择性靶向作用.一项含40名受试者的研究中[321], 随机采用不同参数治疗双眼(560nm和16mJ/cm² vs 590nm和14mJ/cm²), 结果显示两组疗效与患者满意度无显著差异, 但较短波长和较高能量滤光片的实验组报告的不适感更轻.另一项前瞻性随机双眼对照试验发现, 590nm滤光片与痤疮专用滤光片对眼表指标,睑板腺功能及主观症状的改善效果相当[322].比较研究显示, 采用"优化脉冲技术"(无脉冲尖峰)三次治疗与"调控脉冲光"(规则脉冲序列)四次治疗均能改善体征症状达三个月, 但前者在下睑睑板腺功能及部分泪膜指标提升方面更具优势[323].需注意的是, 该研究未设对照组且随访期较短.

多项研究分析了 IPL 治疗后细胞因子水平的变化.一项包含13名受试者的 RCT 研究[324]发现, 与热敷联合睑板腺按摩相比, IPL联合睑板腺按摩治疗组的IL-6,IL-6R,IL-1β,IL-13和CCL11/Eotaxin水平下降更为显著.两组患者的泪液细胞因子水平均较基线显著降低.

除 MGD 患者外, 研究证实 IPL 治疗对以下疾病患者同样有益, 包括睑缘炎相关角结膜炎[325],干燥综合征[326],青光眼相关干眼病[327],屈光手术后干眼病[328],移植物抗宿主病[329]以及神经病理性疼痛[330,331].

除单独使用 IPL 外, 多项研究报道了联合治疗方案对干眼病患者的积极疗效, 包括 IPL 联合0.05%CsA [332],地夸磷索[333],多西环素[334],血液提取物滴眼液[330],热脉动[335,336],加热眼罩[337,338]以及微海绵睑缘去屑术[339].

目前有多家公司生产 IPL 设备, 使用时必须参考具体仪器的用户手册及各厂商的注意事项.IPL治疗通常禁忌用于以下情况:孕妇或哺乳期妇女,佩戴心脏起搏器或除颤器的患者,糖尿病患者,癫痫或血友病患者,近期或计划接受放疗/化疗者,深色皮肤(Fitzpatrick量表VI型)人群,有日光过敏史者,近期接受美黑护理(乳霜或美黑舱)者, 以及使用多西环素和四环素等光敏性药物的患者[340].儿童,前葡萄膜炎或青光眼睫状体炎危象患者也应避免 IPL 治疗[341].治疗区域存在活动性皮肤感染/炎症(如湿疹),纹身,永久性眼妆,唇疱疹,开放性伤口或擦伤时需谨慎操作.治疗前需清除化妆品/乳霜, 并遮盖治疗区域的痣/色素痣.操作期间患者需佩戴仪器专用眼罩/护目镜, 检查者应配备防紫外线护目镜.治疗室外需设置警示标识, 避免他人意外暴露于高强度光源下.有研究报告在严格控制的条件下, 未使用防护眼罩直接对眼睑进行 IPL 治疗可获得初步积极效果[342], 但该结果仍需通过其他 IPL 仪器或方案验证.需注意的是, 上述注意事项并未涵盖所有情况, 目前文献尚缺乏统一的 IPL 禁忌症与注意事项标准.

总之, 大多数关于 IPL 治疗 MGD 相关干眼病的研究表明, 该疗法能改善患者的症状和体征, 但其疗效程度和持续时间因联合治疗方案和治疗次数的不同而存在较大差异.此外, 不同仪器和治疗方案之间也可能存在效果差异.目前仍需要开展独立,大规模,随机对照的长期研究以确定最优治疗方案, 并预测哪些患者可能获益最大.

低能量光疗法(LLLT:红光)

低能量光疗法(LLLT)是通过发光二极管发射低功率,高能量密度的单色或准单色光(如红光,黄光,蓝光等不同波长)进行治疗的技术.LLLT的作用机制被认为是通过光生物调节过程发挥作用[343], 该过程是一种由特定波长的光通过光受体分子激活的非热生物过程, 从而诱导一系列生理级联反应.

在这一过程中, 主要的光感受分子是细胞色素c氧化酶(线粒体呼吸链中的一种酶).当该酶吸收光子后, 会发生氧化还原变化, 从而增强线粒体活性, 促进细胞的主要能量分子三磷酸腺苷的生成[344,345].此外, 光生物调节还能诱导一氧化氮从细胞色素c氧化酶上解离, 减轻一氧化氮对线粒体呼吸的抑制作用, 从而改善细胞能量代谢[346,347].该过程还会在可控水平上产生ROS, 作为第二信使激活信号通路[348].综合这些机制, LLLT被认为具有

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促进组织修复,缓解疼痛和抗炎等治疗作用.通过精确调控波长,强度和能量剂量等参数, 光生物调节可以在不损伤组织的情况下精准调节细胞反应[343,346,348,349].

这种光生物调节技术最初应用于皮肤科, 现已被证实对导致干眼病的眼睑疾病以及眼表和眼周区域的其它炎症性疾病具有疗效.目前关于LLLT作为独立治疗手段的研究数量有限, 且使用的设备,光参数和临床方案各异, 但眼科文献中多数研究采用了eye-light®设备(Espansione集团, 意大利)[350–354].一篇综述指出, 目前尚缺乏明确证据表明单独使用LLLT对治疗 MGD 具有显著益处[355].

一项 RCT 试验将每周两次,持续三周的LLLT治疗与假治疗组(每组n=20)进行比较, 结果显示LLLT组在荧光素和丽丝胺绿眼表染色, Schirmer 试验,上睑睑板腺缺失评分方面表现更优, 但在TBUT ,眼睑肿胀,睑缘毛细血管扩张,睑酯分泌及排出能力评分方面无显著差异[350].另一项研究对30名轻中度干眼病患者进行了每周一次,每次15分钟的eye-light®设备3次LLLT治疗后, LLLT组在NIBUT, TMH ,LLT, OSDI 评分, Schirmer 试验,睑酯质量评分及眼睑温度等指标上均有显著改善[354].

LLLT与 IPL 的关键区别在于LLLT可直接作用于眼睑且不受肤色限制, 适用于所有皮肤类型.一项 RCT 结果显示, 虽然LLLT和 IPL 均能安全缓解眼部不适, 但LLLT在症状改善和泪液量增加方面效果更显著[351].

多项研究使用eye-light®设备将 IPL 与LLLT联合治疗 MGD 患者[356–360], 其中一项多中心回顾性研究对460只传统治疗无效眼采用联合方案:先在眼周施加强脉冲短光, 再以红光照射面颊和眼睑(1~2周间隔, 共2~4次).治疗后 OSDI 评分显著降低, 70%患眼 MGD 分级改善≥1级(28%改善≥2级), TBUT≤6秒的比例从86.7%降至33.9%[360].

目前, 尚未明确LLLT的长期疗效和最佳治疗方案, 且通常认为其与其他干眼病治疗方法联合使用时效果最为显著.还需要更多研究来确定光生物调节作用与其他可能机制(如治疗设备中发光二极管阵列产生的热量)对 LLLT 疗效的贡献[355].

等离子体治疗

针对 MGD 继发的蒸发过强型干眼病, 等离子治疗通过将等离子直接作用于上下眼睑发挥治疗作用[361].该技术利用电离环境气体产生等离子体活性介质, 在低温下将目标组织表层从固态转化为气态[362].目前关于其治疗干眼病效果的证据有限.一项纳入20名 MGD 患者, 但未设置对照组的队列研究报道等离子治疗后的干眼症状较基线有所改善(未提供统计数据), 但泪膜稳定性和泪液分泌量未见持续改善[361].

量子分子共振电疗法

量子分子共振是一种通过低频高强度电流作用于特定生物组织的技术.体外研究表明, 电刺激可促进细胞迁移和增殖[363].多项研究探讨了其在干眼病患者中的应用[364–369], 其中一项针对混合型干眼病患者的病例系列研究采用标准治疗方案(每周一次, 每次20分钟, 持续4周), 结果显示 OSDI ,NIBUT,角膜染色及睑板腺指标均有改善, 且 MMP-9 水平降低[367].此外, 该疗法对 MGD 相关干眼病患者也有效[364].近期研究还表明量子分子共振对难治性干眼病患者具有疗效[365], 但随访时间仅为治疗后两周.一项为期两年的双盲 RCT 中, 40名患者(每组20人)每周接受一次量子分子共振设备治疗或安慰剂治疗, 疗程为4周[369].结果显示干预组 OSDI 评分, MGD 评分和角膜染色显著改善, 而安慰剂组的 OSDI 无明显改变, 但两组间 TBUT ,视力及 Schirmer 评分无显著差异.该技术还需通过长期随机试验进一步评估其实际应用价值.

射频治疗

射频是一种电磁波, 其利用振荡场使目标组织内的粒子带电, 通过振动组织颗粒之间的摩擦产生热量[370].一项涉及10名 MGD 患者的初步研究比较了LipiFlow与ThermaLid®射频(Pellevé皱纹减少系统, Ellman International公司, 美国)的效果[370].治疗三个月后, 两者在改善睑板腺分泌物,蜡样脂栓评分, SPEED 和 OSDI 评分方面效果相似.射频组的Marx线评分在三个月后有所下降, 但两组在NIBUT,角膜染色,泪液渗透压或 Schirmer 试验方面均未明显改善.此外, 一项纳入31名患者的队列研究表明, 射频治疗联合 IPL 和睑板腺按摩可显著改善 MGD 的症状和体征, 但该研究未设置对照组[371].

目前尚无强有力的证据支持射频用于治疗干眼病, 未来需要更多研究, 尤其是更大样本量和更长随访期的 RCT 研究, 以更好地理解该技术的作用机制及其在干眼病治疗中的适用场景.

热机械皮肤治疗

热机械点阵皮肤治疗(Tixel, Novoxel, 以色列)是一种新型疗法, 于2021年获FDA批准用于皮肤美容领域[372].眼周治疗采用400°C钛制探头, 其表面为24个金字塔形凸起矩阵, 每次接触皮肤5至18毫秒, 覆盖面积0.3cm².据报道, 该设备可减少眼周皱纹,玫瑰痤疮,酒糟鼻,血管瘤及瘢痕, 并可能促进透皮给药[372].但目前仅有开放标签试验报道其在蒸发过强型干眼病中作为非消融治疗安全有效[373,374].一项制造商赞助的前瞻性,研究者设盲的研究表明, Tixel的临床效果与热脉动疗法相当[375].

值得注意的是, 近期一项由行业资助的研究报道了在该治疗后, 眼镜屈光度的改变具有统计学和临床意义, 且干眼病越严重变化越明显[376].基于此, 作者建议, 若计划在屈光手术前进行生物测量评估, 需谨慎使用该疗法[376].

睑缘治疗. 睑板腺导管内探通术

睑板腺导管内探通术使用直径76μm,长度有1mm,2mm,4mm,或6mm的不锈钢钝头探针, 通过机械疏通阻塞的睑板腺以促进睑酯分泌[377].当探针遇到阻力时可能听到"噗噗"声.自 TFOS DEWS II 管理及治疗报告发布以来[2], 已新增多项研究使用该技术用于治疗MGD, 包括三项 RCT 及多项回顾性和/或非随机研究.

在一项前瞻性研究中, 对30名 MGD 患者的58只眼进行改良探通术治疗(1—4次), 所有患者同时接受抗生素,皮质类固醇,人工泪液,热敷及睑缘按摩等辅助治疗[378].三个月后, TBUT,结膜充血,睑缘血管化及 OSDI 评分显著改善, 但难以区分探通术与其他辅助治疗的效果.

一项回顾性病历研究纳入108名阻塞性 MGD 患者(共11,776个腺体), 发现84%的腺体存在机械阻

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力[379].然而, 这种阻力的临床相关性及其与腺体分泌功能的关系尚未完全阐明.

另一项回顾性研究分析使用1mm探针对38名患者的下睑进行睑板腺成像引导探通, 解决了一些围绕该技术的侵入性及其对睑板腺脆弱结构损害的潜在担忧.结果显示99.9%腺体(996/997)成功探通, 91.8%可清晰显示探针位置[380].此外, 一项基于共聚焦显微的回顾性研究探究了探通术后的睑板腺导管显微结构改变, 比较了16名 MGD 患者(共36个上睑腺体)与4名未接受探通治疗 MGD 患者的腺体微结构, 发现探通组基底膜,导管壁的层次,厚度, 以及管腔面积增加[381], 提示该技术可能刺激上皮再生, 但具体机制需进一步研究.

2020 年的一项文献综述纳入了 14 项研究, 其中大部分(10/14)缺乏对照组[382].研究发现导管内探查术具有一定安全性, 无严重术后并发症.然而, 眼睑及腺体开口处出血(点状出血)较为常见, 但具有自限性.TBUT是最常见的客观测量指标, 多数研究显示该指标改善, 但唯一一项随机假对照试验发现两组间无差异 [383].由于部分研究采用辅助治疗(抗生素,类固醇,强脉冲光), 可能对 TBUT 的结果产生影响.在这14项研究中, 有5篇研究将角膜染色作为结局指标, 但与 TBUT 类似, 由于采用了辅助治疗, 其结论仍不明确.该术式的发明者对该综述的结论持不同意见, 并就其中部分结论撰写了反驳信[384] .

近年来发表了三项关于睑板腺导管内探通的 RCT 研究.一项研究显示, 与传统治疗(人工泪液,热敷,眼睑按摩,睑缘清洁,局部抗生素,ω-3补充剂和口服阿奇霉素)相比, 导管内探通联合传统治疗在90天内治疗效果更优(OSDI评分, Schirmer 试验, TBUT 和牛津分级), 但睑酯排出能力未见明显改善[385].另一项研究将45名阻塞性 MGD 患者的90只眼分为三组:IPL组(三次治疗, 间隔三周),单纯睑板腺导管内探通组, 以及探通后 IPL 联合治疗组[386].所有组别均显示改善, 探通-IPL联合治疗组在改善患者主观症状(SPEED评分)和客观体征(TBUT,角膜荧光素染色,睑酯性状)方面均显著优于单一治疗组和对照组.唯一一项双盲 RCT 研究(未联合其他治疗)显示, 导管内探通显著改善症状, 但在临床体征方面与安慰剂相比无差异[383].

综上所述, 基于相对短期的结果, 睑板腺导管内探通术是一种有自限性并发症的治疗手段.未来需要前瞻性 RCT 研究, 尤其是在无联合治疗的情况下进行评估, 以更好地理解其在改善症状,体征,睑板腺导管完整性和睑酯分泌能力方面的作用机制.睑板腺成像引导下的导管内探通术可能为阻塞性 MGD 的治疗提供额外价值, 但需更大样本量和长期随访研究以评估腺体结构完整性.

睑缘清洁

睑板腺阻塞主要由于角化物质在睑缘和睑板腺开口处堆积所致[167,227].这种堆积会阻塞腺体, 阻碍睑酯分泌到泪膜中.睑缘清洁通过物理清除睑缘表面堆积的碎屑和角化细胞, 从而促进腺体分泌睑酯进入泪膜[387].两项为期一个月的 RCT 研究报告显示, 与未治疗的对照组相比, 睑缘清洁可改善症状和睑板腺分泌功能[387,388].

一种新型多模式热疗设备 (MGrx, OcuSci®, Inc, CA, 美国)已被开发用于辅助热疗睑缘清创,热疗眼睑按摩以及热疗腺体挤压.一项开放试验研究纳入了 37 名 MGD 和干眼病成年患者, 接受MGrx治疗[389].经过治疗后, 患者双眼的 SPEED 评分, TBUT 和睑板腺评分均显著改善, 且无不良反应报道.随后开展的 RCT 研究发现, 传统治疗与MGrx治疗在症状改善方面效果相似, 但临床体征未显著改善[390].

一项回顾性病例系列研究报道, 睑缘清洁联合微海绵睑缘去屑 (BlephEx®;RySurg, Fort Worth, FL, 美国)及睑板腺挤压治疗可改善患者临床结果,主观症状,睑板腺功能和眼表 MMP-9 水平[391].然而, 目前仍缺乏假治疗对照和双盲设计的前瞻性研究.

- 泪液恢复或分泌刺激:

局部促分泌剂

地夸磷索钠

3%地夸磷索滴眼液通过刺激泪液和黏蛋白分泌发挥作用[392].其作为P2Y2嘌呤受体激动剂, 可激活眼表的P2Y2受体.地夸磷索钠通过与P2Y2受体相互作用, 直接刺激结膜上皮细胞分泌液体和结膜杯状细胞分泌黏蛋白[392,393].

针对此类药物已开展多项长期研究 (表 3). 一项纳入14项 RCT 研究的 Meta 分析表明, 与使用其他局部滴眼液(如人工泪液或透明质酸类产品)的受试者相比, 使用3%地夸磷索滴眼液治疗4周后, TBUT, Schirmer 评分,角膜荧光素染色评分和玫瑰红结膜染色评分均显著改善[394].但在 OSDI 症状评分方面未发现明显差异[394].

在一项纳入47名 MGD 患者的研究中, 每名患者的双眼分别随机滴入人工泪液或地夸磷索.结果显示, 地夸磷索可显著增加 LLT 和 NIBUT, 且作用持续至少90分钟, 而人工泪液无此效果[395].该研究结果表明, 地夸磷索不仅可能适用于治疗水液缺乏型干眼病, 也可能对与 MGD 相关的蒸发过强型干眼病具有治疗潜力.

口服促分泌剂

早期文献报道口服毛果芸香碱和西维美林在干眼病治疗中的应用, 尤其针对与干燥综合征相关干眼病患者[2].毛果芸香碱和西维美林均为胆碱能激动剂, 可模拟乙酰胆碱神经递质作用, 选择性靶向M1-M3型毒蕈碱受体.

自2017年 TFOS DEWS II 管理与治疗报告发布以来[2], 因为口服促泌剂主要作用于唾液腺, 大多数研究均纳入干燥综合征患者.一项安慰剂对照交叉研究表明, 每日四次口服5mg毛果芸香碱, 可改善 OSDI 评分,NIBUT, TBUT 和 Schirmer 评分,眼表染色和泪液蕨样试验分级, 但药物导致的不良反应发生率较高[409].需要注意的是, 口服促分泌剂会同时刺激其他外分泌腺的毒蕈碱受体, 可能导致多汗,流涎,尿频,潮红,感觉异常和肌痛等副作用[409–412].国家处方报告(如国家卫生和保健研究所)还记载了未在临床试验中报道的其他副作用, 包括出汗,恶心,心动过缓,支气管痉挛,腹泻,头痛和视力障碍.

- 黏蛋白的恢复或刺激: 多种药物通过增加泪液黏蛋白发挥作用.

地夸磷索钠

如前述(见第6.3.2.1.1节), 地夸磷索可刺激眼表黏蛋白生成[392,393].

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表 **3.** 评估地夸磷索钠有效性和安全性的前瞻性研究

研究	患者类型	治疗	产品对照	样本量	持续时间	随机化	疗效改善指标	与对照无显著差异的结果
Miyake 和Yokoi, 2017 [396]	白内障术后4周	Diquas 3%	人工泪液	433	1个月	是	TBUT 总症状评分	角膜染色 结膜染色
Shimazaki 等, 2017 [397]	电脑使用者干眼病	Diquas 3%	瑞巴派特	67	2个月	是	满意度评分	DEQS BUT NIBUT 角膜染色
Cui 等, 2018 [398]	白内障术后干眼病	Diquas 3%	0.15%透明质酸	94	3个月	否	OSDI TBUT 杯状细胞密度	Schirmer 试验
Kaido 等, 2018 [399]	短 TBUT 干眼病	Diquas 3%	人工泪液	27	5周	否	角膜敏感度 TBUT	泪河高度
Jun 等, 2019 [400]	白内障术后干眼病	无防腐剂 Diquas 3%	a)含防腐剂 Diquas 3% b) 0.15%透明质酸	117	3个月	否	TBUT MGD 分级 睑酯质量	OSDI 角膜染色
Fukuoka 和Arita, 2019 [395]	MGD 相关干眼病	Diquas 3%	人工泪液	47	90 分钟	是	NIBUT 泪膜脂质层厚度	-
Ji 等, 2019 [401]	干眼病	Diquas 3%	0.05% CsA	18	1个月	否	泪液蛋白质组	OSDI TBUT Schirmer 试验 角膜染色 结膜染色
Kim 等, 2021 [402]	白内障术后干眼病	Diquas 3%	0.15%透明质酸	56	15周	是	泪膜脂质层厚度 TBUT	OSDI Schirmer 试验
Eom 和 Kim, 2021 [403]	干眼病	Diquas 3%	0.1% CsA或联合治疗	279	3个月	否	TBUT	SANDE DEOS 角膜染色 结膜染色
Yamazaki 等, 2022 [404]	飞秒白内障术后	Diquas 3%	生理盐水	20	2周	是	TBUT	泪河高度DEOS Schirmer 试验 角膜染色
Jung等, 2023 [405]	干眼病	Diquas 3%	0.1% CsA 0.05%CsA	80	3个月	否	泪液蛋白质组	SANDE TBUT 结膜染色
Wang等, 2023 [406]	飞秒 LASIK 术后	Diquas 3%＋0.15%透明质酸	0.15%透明质酸	40	1个月	否	OSDI TBUT 脂质层分级球结膜充血 角膜缘充血	NIBUT **表面规则指数**
Kaido和Arita, 2024 [407]	干眼病	高黏度Diquas 3%	常规Diquas 3%	66	1个月	否	问卷评分 角膜染色	-
Arita等, 2024 [408]	干眼病	高黏度Diquas 3%	常规Diquas 3%	341	3个月	否	TBUT SPEED TBUT 泪河高度 角膜染色 Schirmer 试验	-

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瑞巴派特

瑞巴派特(2-(4-氯苯甲酰胺基)-3-2(1H)-喹啉酮-4-基丙酸;OPC-12759)是一种黏膜保护剂, 通过口服给药的方式治疗胃炎和胃溃疡.研究显示, 瑞巴派特通过刺激COX2和前列腺素生成,清除氧自由基,抑制促炎细胞因子, 在急慢性黏膜炎症中发挥抗炎作用[413].虽然该药物能增加结膜杯状细胞数量, 但其分子作用机制和细胞受体特性尚未完全阐明[414].

表 4 列出了瑞巴派特相关临床试验.研究显示, 1%和2%瑞巴派特干眼病治疗组在TBUT ,角膜染色评分和 Schirmer 评分方面优于安慰剂, 但 OSDI 评分无显著差异[415].一项随机,对照,双盲研究发现, 视频终端导致的眼疲劳患者使用2%瑞巴派特4周后, 较0.1%透明质酸组角膜染色和鼻侧球结膜充血评分显著降低, 但两组在 OSDI ,5项干眼病问卷, TBUT 和结膜染色评分方面改善相似[416].一项纳入7篇关于瑞巴派特治疗干眼病的系统综述指出, 瑞巴派特在角膜荧光素染色,无麻醉 Schirmer 试验, TBUT 和干眼病相关生活质量评分方面优于对照组[417].最新系统性综述和 Meta 分析也证实了这一结论[418].

• 神经调节/神经刺激: 泪膜分泌的刺激是由角膜和结膜的感觉传入神经以及鼻腔副交感神经所感知的环境刺激驱动的.这些感觉神经一旦被激活, 便通过三叉神经以动作电位的形式传递环境信息, 继而触发副交感神经的传出反应, 协调泪腺功能单元(泪腺,睑板腺和杯状细胞)的分泌活动增强[36,423–425].神经调节作为干眼病的一种治疗方式, 通过刺激上述感觉神经以激活三叉神经信号传导, 从而增加包含水液层在内的基础泪液分泌[423,424–427].这种调节可通过机械,电刺激(压力/振动)或药物手段实现.

设备驱动的神经调节

鼻内电化学刺激

通过经皮电刺激鼻黏膜和三叉神经前筛神经支, 可实现经鼻神经刺激, 从而触发鼻泪反射性泪液分泌.FDA曾批准一种鼻内刺激设备(TrueTear®鼻内泪液神经刺激器), 但该产品已于2020年停产[424].然而, 多项研究对该技术的疗效进行评估, 为这一潜在干眼病管理方法提供了有价值的信息.该设备通过在双侧鼻腔中插入两个鼻内探头, 利用低强度电流使探头振动并与鼻内组织接触.一项 RCT 研究比较鼻内与鼻外刺激发现, 单次鼻内刺激3分钟后, 干眼病与非干眼病受试者的泪液分泌(通过测量泪河高度和泪河面积评估)和分泌黏蛋白的结膜杯状细胞密度(通过印迹细胞学评估)均较基线增加[428].在一项方法类似的研究中, 受试者经过3分钟鼻内刺激治疗后, 眼干症状和眼部不适评分于治疗后5分钟显著降低[429].另一项 RCT 研究比较了每日4-8次,每次30秒至3分钟的鼻内刺激与假刺激的效果, 发现在第0,7,14,30和90天的随访评估时, 鼻内刺激组的急性泪液分泌量 (Schirmer 评分)在所有时间点均显著高于假刺激组.早期时间点的急性反应最强(约为假刺激的3倍), 第14天降至约2倍并保持稳定至研究结束.第90天时, 鼻内刺激与假刺激组的角膜和结膜染色评分均较基线有所下降, 但仅鼻内刺激治疗组的疼痛评分显著降低[430].使用该设备可能引发鼻出血,电击样刺痛感,鼻部不适,头痛,眼睑刺激,流涕和牙齿敏感等短暂性不良反应[429–431].此外, 在接受3分钟鼻内刺激治疗的干燥综合征患者中, 也观察到比外部刺激更显著的 Schirmer 评分改善[432].

外部治疗旨在刺激前筛神经的外侧分支.一项多中心开放标签,单臂临床试验使用新型设备(iTear®100)对101名受试者进行每日至少2次,每次30秒的鼻外侧刺激, 结果显示从第14天到第30天 OSDI 评分下降, Schirmer 评分从第14天开始升高并持续至第180天研究结束, 期间未报告严重不良事件[433].

经皮电刺激

高频与低频经皮神经电刺激是一种非药物疗法, 通过皮肤电极直接激活三叉神经末梢分支(位于前额和太阳穴)的外周神经通路来阻断,改变或纠正痛觉感知.该疗法通过置于额头和太阳穴处, 靠近三叉神经末梢皮肤分支的皮肤电极传递交变电流.传入的电信号传递至中枢神经系统, 激活下行抑制系统, 从而减轻痛觉过敏并释放内源性阿片类物质[426,434].电刺激被认为对难治性疼痛患者(如表现为"无染色的疼痛",神经性疼痛,畏光或其他可能与眼痛觉过敏相关的慢性疼痛患者)具有潜在镇痛效果[435–436].

一项纳入45名患者的 RCT 研究比较了含HA人工泪液联合/不联合经皮电刺激的效果, 结果显示治疗4周后, 接受电刺激治疗组在症状评分, TBUT , Schirmer 评分和角膜染色方面均有更显著的改善 [437].另一项纳入27名患者的研究报道, 经皮电刺激治疗6个月后, TBUT和眼表染色评分改善, 12个月后仍能观察到 OSDI 评分降低和 Schirmer 评分升高 [438].

药物性神经调节

Acoltremon

Acoltremon(Alcon公司, Ft Worth, TX, 美国)是一种强效且高选择性的TRPM8激动剂, 其0.003% 浓度的滴眼液(前称AR-15512)目前正处于干眼症状治疗的临床研究阶段, 用于评估其在治疗干眼病体征和症状方面的疗效.

瞬时受体电位 (TRP) 通道超家族成员是阳离子通透的质膜离子通道, 可响应多种刺激[439]. TRPM8 离子通道表达于支配角膜和上眼睑的温度感受神经元, 能在温度小幅度下降和高渗透压(如蒸发冷却或角膜干燥)时激活[423,439–441], 进而激发冷温度感受神经元, 通过三叉神经增强信号传导, 刺激基础泪液分泌[441,442].

目前已完成一项关于Acoltremon的临床试验[443].在这项评估0.0014%和0.003% AR-15512相较其载体的 RCT 研究中, 观察到其在症状和体征方面具有一定的改善作用:眼部不适评分(第84天)和整体 SANDE 评分(第14,28和84天)改善, 泪液分泌增加(未麻醉 Schirmer 评分和泪河高度, 第1和14天), 结膜充血减轻(第84天), 眼表染色评分改善(第14和84天), 其中0.003%剂量组效果显著.报告的不良事件较轻(滴药后灼烧感/刺痛感).对于共同主要观察终点(第28天时眼部不适评分和麻醉后 Schirmer 评分较基线的变化), 载药组与载体组无显著差异[443].

Cryosim-3

Cryosim-3(C3, 1-二异丙基磷酰基壬烷)是一种水溶性选择性 TRPM8 激动剂.局部应用于上眼睑表面

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表 **4.** 瑞巴派特临床对照试验研究

研究	患者类型	治疗	对照产品	样本量	持续时间	随机化	疗效改善指标	与对照无显著差异指标
Kinoshita等, 2013 [419]	干眼病	2% 瑞巴派特, 每日4-6次	0.1%透明质酸, 每日4-6次	188	4周	是	结膜染色 部分症状	角膜染色 Schirmer 试验 TBUT 部分症状
Igarashi等, 2015 [420]	角膜屈光术后干眼病	2%瑞巴派特, 每日4次	人工泪液每日4次	60	4周	是(无直接比较)	Schirmer 评分, TBUT 角膜染色 眼散射指数 部分症状	部分症状
Kobashi等, 2017 [421]	穿透性角膜移植术后干眼病	瑞巴派特	地夸磷索钠	40	4周	是	-	TBUT 角膜染色 症状
Shimazaki等, 2017 [397]	视频终端相关干眼病	2%瑞巴派特, 每日4次	3%地夸磷索钠, 每日6次	79	8周	是	-	症状 TBUT
Eom等, 2023 [415]	干眼病	1%瑞巴派特, 每日4次	安慰剂(载体), 每日4次	220	12周	是	症状 角膜染色(2%荧光素钠组)	TBUT Schirmer 试验 角膜染色(1%荧光素钠组)
Jain等, 2023 [422]	干眼病	2%瑞巴派特, 每日4次	0.5%CMC 润滑剂, 每日4次	80	12周	是	仅进行分类分析	TBUT, Schirmer 试验 角膜和结膜染色
Lee和Han, 2024 [416]	视频终端相关干眼病	2%瑞巴派特, 每日4次	0.1%透明质酸, 每日4次	56	4周	是	角膜染色	症状 TUBT 结膜染色

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时, 可通过激活 TRPM8 受体产生清凉感从而缓解不适.在一项比较C3(溶于 2mg/mL 蒸馏水)与其载体的随机双盲研究中, C3组在用药后5-16分钟症状强度降低, 20,40和60分钟时泪液分泌增加, 30和40分钟时TBUT 延长.两周后症状仍有改善[444].一项探索性试验中, 患者每日接受C3治疗4次, 持续1个月, 结果显示治疗终点 Schirmer 评分升高而眼痛评估调查评分降低[445].根据现有公开信息, 该药物目前尚无正在进行的临床试验.

伐尼克兰

伐尼克兰(OC-01)以鼻喷雾剂形式给药, 其治疗机制为靶向鼻腔内的烟碱型乙酰胆碱受体.鼻黏膜与眼表的三叉神经伤害感受器构成调控泪液生成的传入通路起始端.当药物刺激鼻神经末梢的烟碱型乙酰胆碱受体时, 会刺激内源性泪液分泌[425].该鼻喷雾剂(Tyrvaya®;Oyster Point Pharma, 新泽西州, 美国)已获FDA批准用于治疗干眼病.

为研究伐尼克兰对结膜杯状细胞的影响, 一项II期单中心载体对照试验纳入18名干眼病患者[446].受试者按2:1随机分配, 接受每侧鼻腔喷入50μl 0.06 mg OC-01或载体鼻喷雾.结果显示, OC-01治疗组杯状细胞平均面积和周长均减小, 而载体组无此效应, 提示其促进杯状细胞脱颗粒及黏蛋白释放[446].

一项 RCT 研究评估了不同浓度伐尼克兰与缓冲盐水的疗效比较, 结果显示每日2次使用0.03 mg剂量的伐尼克兰治疗至第28天时, 可显著降低眼干症状评分[447].同一研究团队开展的另一项研究表明, 使用0.03 mg伐尼克兰治疗12周能有效提高 Schirmer 试验评分[447].此外, 其他研究者使用0.06 mg浓度也观察到相似的治疗效果[448,449].

一项III期临床试验结果显示, 伐尼克兰OC-01改善Schirmer 评分和症状的效果与立他司特相当或更优[450], 且伐尼克兰耐受性良好, 患者研究完成率>93%[451], 但几乎所有OC-01受试者治疗期间至少出现过一次喷嚏反应(0.03 mg组93.8%, 0.06 mg组95.9%, 载体组28.3%), 多数喷嚏(0.03 mg组84.5%, 0.06 mg组81.3%)发生在给药后1分钟内[452].

一项系统综述和 Meta 分析纳入3项 RCT 研究(共1063名受试者), 比较伐尼克兰鼻喷雾与安慰剂治疗干眼病的有效性和安全性[453].结果显示, 第28天时 Schirmer 评分均值较基线显著增加, 伐尼克兰与安慰剂组的眼部不良事件发生率无显著差异, 但使用伐尼克兰治疗显著增加鼻腔相关不良反应(咳嗽和咽喉刺激)风险[453].最新的系统综述共纳入8项研究, 发现伐尼克兰鼻喷雾在眼干评分, Schirmer 试验和总角膜荧光素染色方面较载体改善更显著[454].

表 5 详述了伐尼克兰相关的重要临床研究.

表 5. 伐尼克兰临床试验研究比较

研究	患者类型	治疗	对照方案	样本量	持续时间	随机化	疗效改善指标	与对照无显著差异指标
Dieckmann等, 2022 [446]	干眼病	OC-01 0.06mg 每日1次	载体鼻喷雾	18	单次给药	否	结膜杯状细胞面积和周长减小	睑板腺面积
Quiroz-Mercado等, 2022 [448]	干眼病	OC-01 0.03 mg 0.06 m每日2次	载体鼻喷雾 每日2次	123	12周	是	Schirmer 评分	-
Torkildsen等, 2022 [455]	干眼病	OC-02 Simplniciline 0.11 mg, 0.55 mg, 或1.1 mg	载体鼻喷雾	165	单次给药, 用药后5分钟	是	症状(0.55 & 1.1mg) Schirmer 评分	-
Witta等, 2022 [447]	干眼病	伐尼克兰OC-01 0.006mg, 0.03mg, 0.06mg 每日2次	载体鼻喷雾 每日2次	182	4周	是	症状(0.03mg) Schirmer 试验(0.03和0.06mg组)	-
Witta等, 2022 [452]	干眼病	伐尼克兰OC-01 0.03mg 0.06mg 每日2次	载体鼻喷雾 每日2次	758	4周	是	症状 Schirmer 评分	-
Tian等, 2024 [456]	干眼病	OC-01 0.6 mg/mL 每日2次	载体鼻喷每日2次	340	4周	是	症状 Schirmer 评分	角膜荧光素染色

眼睑异常的治疗

眼睑是泪液功能单元的重要组成部分, 正确识别并矫正睑缘异常是干眼病治疗的关键环节.自2017年 TFOS DEWS II《管理与治疗报告》发布以来[2], 已有许多研究探讨了针对眼睑疾病的新兴治疗策略.

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这些治疗方式可分为以下大类:

家庭治疗: 包括热敷(需配合睑板腺按摩以达到最佳效果)[232,235–237,239,241,242,256]以及多种睑缘清洁湿巾[231,457,458].

临床治疗:涵盖IPL [230],矢量热脉动治疗[282],低强度光疗法[351],微海绵睑缘去屑术[459],热机械治疗[373,374],便携式445nm激光[460],多种眼睑及睑板腺手动热传导技术[240,285,289],睑板腺探通术[382,461]以及睑板腺挤压术[462].

药物治疗:如洛替拉纳[463,464]和伊维菌素-甲硝唑凝胶[465], 这类药物针对寄生虫性睑缘炎, 可改善患者症状,泪膜及眼表参数.正在进行注册临床试验的其他MGD 药物治疗策略包括硫化硒[271]和阿奇霉素[466].

下文将根据疾病临床表现, 阐述这些疗法在临床应用中相关证据.

• 眨眼及眼睑闭合异常: 改善眨眼频率及强调完全性眨眼是治疗干眼病中最简易的干预手段之一, 但可能是最难有效执行的方法之一.现有网络平台及软件程序可监测患者使用电子设备时的眨眼频率, 并提醒患者有效眨眼[467].

眼睑闭合不全/兔眼症

眼睑闭合不全指眼睑无法完全闭合, 而夜间眼睑闭合不全特指在清醒状态下可正常闭眼, 但在睡眠时发生的眼睑闭合不全[468].眼睑闭合不全是难治性干眼病的主要诱因之一[469].日本一项研究调查了2000名受试者夜间眼睑闭合不全发生率与睡眠质量的关系[6].根据是否存在干眼症状将受试者分组, 结果显示:干眼病组睡眠时间显著缩短,睡眠效率更低;夜间眼睑闭合不全的受试者在干眼病组中占比更高.研究结论认为, 夜间眼睑闭合不全与干眼症状加重及睡眠质量下降相关[6].

以下情况均可导致眼睑闭合不全:松弛性眼睑综合征,美容手术及化学去神经注射,眼睑畸形,贝尔面瘫,年龄相关性眼睑松弛,皮肤松弛症,老年性睑外翻,外伤,Graves病及解剖结构异常[468,470].睡眠时泪液分泌减少, 眼睑闭合是保护眼球避免干燥的基础条件[471].因此, 建议眼睑闭合不全患者夜间使用眼膏[472].

尽管有零星报道, 但目前尚无研究评估夜间使用胶带粘贴眼睑的效果.患者对此类治疗的耐受性可能有限, 原因包括:眼睑组织反应风险,老年人夜间频繁如厕的不便, 以及撕除胶带时可能导致睫毛脱落.近期已推出新型眼睑闭合产品, 其特点为低致敏性,无乳胶,透氧且不粘连睫毛.

睡眠眼罩可通过限制空气流动减轻环境因素对眼表的干燥刺激, 从而发挥一定作用[473].相比之下, 湿房镜可能更具优势, 因其在限制气流的同时能维持湿润环境(参见第6.2.2节).

多项研究探讨了使用治疗性软性角膜接触镜, 尤其是巩膜镜在处理慢性暴露性眼病的疗效[199,474–480].如Jacobs团队所述[199], 尽管有大量关于暴露性眼病治疗的文献, 但提及接触镜作为治疗选择的较少, 提示其作用可能被低估.

甲状腺眼病也可因眼球突出和眼睑退缩导致暴露性眼病[13,472,481–483].一项保守治疗研究(采用人工泪液润滑,冷敷,睡眠时抬高床头,夜间贴闭眼睑及戒烟等措施)显示:轻度病例随访时症状减轻且满意度提升, 中度病例需加用局部激素, 重度病例需手术干预, 但研究中未提供支持性数据[482].另一项研究发现激素冲击联合眶部放疗6个月后患者眼球突出度,临床活动评分及 MGD 改善, 但其他干眼病参数无变化[484].

新型抗IGF-1R抗体疗法(替妥木单抗, Tepezza®, 安进制药, 美国)可改善复视,眼球突出,泪液分泌不足及视功能[485,486], 在甲状腺眼病治疗中展现出前景, 但可能引发高血糖,腹泻,听力损失及皮肤黏膜干燥等不良反应[487].鉴于甲状腺眼病患者普遍存在干眼病, 且该疗法能减轻眶部炎症, 需进一步研究以评估抗IGF治疗对眼表健康的影响.

对于甲状腺眼病导致的严重眼睑闭合不全(如上睑退缩), 可采用外侧睑板结膜瓣,睑切开术或肉毒素注射等方案减轻眼表损伤, 但尚缺乏不同术式的疗效比较[488].

对于严重眼睑闭合不全(如创伤或疾病导致的面瘫患者), 手术选择包括暂时性或永久性睑缘缝合术,上睑退缩时的上睑配重植入术, 以及针对下睑退缩的外眦成形术(可联合或不联合中板层间隔物), 但目前尚缺乏不同术式间的比较研究[489–491].一种新型治疗方法采用自体脂肪移植进行上睑填充, 避免了传统配重植入术可能导致的移位风险.在一项针对75例单侧面瘫患者的上睑脂肪移植研究中, 结果显示该方法能立即改善角膜不适症状, 并获得良好的美学和功能效果[492].

不完全眨眼

无论眼睑形态如何, 不完全眨眼和眼睑错位都十分常见[493], 导致干眼病风险增加2.2倍[494].不完全眨眼患者的OSDI 评分更高, 睑板腺缺失更显著, MGD体征更明显, LLT更薄, NIBUT更短[494].值得注意的是, 该研究发现眨眼频率与任何眼表参数均无相关性[494].完全眨眼时, 随着泪膜的分布, Riolan肌收缩会对睑板腺施加压力, 被认为有助于将睑酯从腺体排出至眼表[167].据推测, 不完全眨眼导致的睑酯分泌减少会产生长期影响, 包括睑板腺阻塞和缺失, 从而持续减少眼表脂质分布[494].研究表明, 有意识地重复用力眨眼可以增加泪膜脂质层厚度[495],延长NIBUT, 并改善干眼症状和眨眼完全性[496].

向干眼病患者提供眨眼训练指导及完全眨眼技巧的教学, 可有效缓解其症状[496,497].此外, 促进眨眼频率增加的技术手段(如为电脑使用者设计的动画提醒)已被证实能够减轻干眼症状[498,499].

• 降低眼睑微生物负荷的方法: 前部睑缘炎是一种慢性眼睑炎症, 主要累及睫毛根部,毛囊(边缘性睑缘炎)和/或眼睑皮肤(眼睑皮炎), 其特征常表现为红肿,皮疹,溃疡,结痂和肿胀[35,500,501].

虽然确切病因尚不明确, 但很可能是多种因素导致的, 包括眼表细菌的慢性低度过度定植,寄生虫感染以及脂溢性皮炎等炎症性皮肤病.睑缘炎可通过多种方式进行分类[500–502], 可根据病程长短(急性或慢性)或致病因素进行分类, 前部睑缘炎可分为葡萄球菌性(细菌性),脂溢性或蠕形螨感染[500,501,503–506].前部睑缘炎的治疗应根据潜在病因, 通常以降低眼睑微生物负荷为目标.尽管可能存在睑缘有微生物负荷而无明显症状的情况[507], 但研究表明降低睑缘微生物负荷具有治疗作用, 许多前部睑缘炎的治疗方法都基于这一原理.

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抗蠕形螨治疗

多项研究证实蠕形螨感染与前部睑缘炎存在明确关联[36,508,509].值得注意的是, 蠕形螨也可存在于健康人群的眼睑, 其感染率随年龄增长而升高, 且在干眼病, MGD ,青光眼及角膜接触镜佩戴者中更为常见[506,508,510–514].

既往研究指出[515], 为利于研究间比较, 当前蠕形螨研究中有诸多需要规范化的环节, 包括标准命名(圆柱状鳞屑 vs 袖套样分泌物),螨虫采集方法(拔睫毛 vs 睫毛旋转/操作)以及螨虫鉴定方法(活体 vs 离体检测).

对于有症状患者, 当睫毛出现圆柱状鳞屑/袖套样分泌物时(此为蠕形螨感染的特征表现[511,514–516]), 可推测蠕形螨是主要诱因[514].鉴于螨虫生命周期约为14-23天[509,517], 治疗可能需要持续数周以覆盖生命周期各阶段的螨虫.现有治疗方案多样, 涵盖非处方家庭疗法至处方滴眼液,眼膏及全身用药等.

目前关于蠕形螨睑缘炎诊断与治疗已有专家共识发布[518].该共识由眼科护理专家小组制定, 推荐将含TTO的眼睑清洁湿巾作为家庭一线治疗方案.专家们建议治疗周期维持4-6周, 每日两次, 并在治疗开始后2-6周进行随访评估, 必要时转为二线治疗[518].

实施眼部蠕形螨治疗时需谨慎, 治疗目标不是一定要完全清除螨虫, 而是通过减少螨虫数量使睑缘生态恢复至共生的平衡状态[505].研究表明蠕形螨可能通过调节细菌活性,抵御其他螨虫而发挥生态作用[505], 德尔菲专家小组也一致认为, 无需彻底根除螨虫[514].关于蠕形螨性睑缘炎治疗的成功标准, 专家建议可通过以下指标评估:眼睑瘙痒完全消失,无眼睑红斑或极轻微,症状减轻以及袖套样分泌物减少[514].

尽管多项研究证实蠕形螨的存在与 MGD 及干眼症状体征具有相关性[519–524], 但迄今尚无经同行评议的证据表明蠕形螨会直接导致干眼病或 MGD .该因果关系的确立需要更多证据来直接阐明螨虫存在与 MGD 发病机制的联系.

伊维菌素. 伊维菌素是一种广谱抗寄生虫药, 最早于20世纪70年代从阿维链霉菌(Streptomyces avermitilis)中提取获得[525].作为口服制剂时, 即使在大剂量使用情况下, 伊维菌素仍显示出良好的安全性[526], 同时能有效降低蠕形螨负荷并改善泪膜稳定性[2,527,528].局部用伊维菌素制剂可直接作用于感染部位, 被认为是一种更高效的治疗方案[529], 虽已证实其疗效显著, 但部分患者会出现明显不适感[529–532].

一项研究比较了单纯使用TTO清洁产品与局部用1%伊维菌素乳膏的疗效.治疗组每周一次将乳膏涂抹于上下睑睫毛, 15分钟后用眼睑清洁剂清除.结果显示, 伊维菌素组在症状改善,眼表染色,睫毛碎屑,红肿以及毛细血管扩张等方面均显著优于对照组[530].

另一项针对75例眼蠕形螨病患者的研究中, 受试者连续三个月每晚在双眼睑缘涂抹1%伊维菌素乳膏[532].治疗后, 受试者的有圆柱状鳞屑/袖套样分泌物的睫毛数量及比例,可见螨尾的睫毛比例以及毛囊口隆起程度均显著降低.此外, 角膜荧光素染色严重程度评分较基线显著改善.仅2例患者出现用药部位皮肤刺激和灼痛感.

一项为期六年的回顾性研究纳入2157例(4314眼)蠕形螨性睑缘炎患者, 所有患者接受每日一次1%伊维菌素局部治疗, 疗程为两个月[531].治疗后, 圆柱状鳞屑/袖套样分泌物和结膜充血显著减少, OSDI评分明显改善.所有患者随访六个月, 其中312例(14.4%)因症状复发接受第二个疗程治疗.14例(0.6%)报告眼部不适和刺激症状.最新 Meta 分析显示, 伊维菌素与甲硝唑联用可显著减少螨虫数量[533].

洛替拉纳滴眼液. 0.25%洛替拉纳滴眼液(XDEMVY®;Tarsus制药, 美国)是目前唯一获得FDA批准用于根除眼部蠕形螨的药物.洛替拉纳是一种选择性作用于螨虫的γ-氨基丁酸门控氯通道抑制剂, 通过阻断这些氯通道导致靶生物体麻痹死亡[534].该滴眼液的亲脂特性可能有助于其被睫毛毛囊(螨虫主要栖息部位)的油性皮脂吸收[534–536], 治疗方案为每日2次,持续6周以覆盖螨虫生命周期.

两项III期临床试验(SATURN-1和 SATURN-2)在883例受试者中评估了0.25%洛替拉纳滴眼液的疗效(基于圆柱状鳞屑/袖套样分泌物减少)和安全性[464,536]. SATURN-1研究显示, 治疗第43天时, 洛替拉纳组袖套样分泌物≤ 2处的患者比例显著高于对照组(44% vs 7.4%)[536], ≤ 10处的比例分别为81.3% vs 23%. SATURN-2 研究同样显示, 洛替拉纳组与对照组袖套样分泌物≤ 2处和≤ 10处的比例分别为56% vs 12.5%和89.1% vs 33.0%[464].此外, 96.4%的治疗眼在六周后袖套样分泌物至少改善1级.随访观察1年的长期疗效数据显示, 接受0.25%洛替拉纳滴眼液治疗的患者中, 维持≤ 2处及≤ 10处袖套样分泌物的比例均显著高于安慰剂组[537].

III 期临床试验中第43天的螨虫根除率评估显示, 在 SATURN-1 研究中, 洛替拉纳组的完全根除率(0螨虫/睫毛)达67.9%, 而对照组为17.6% [536]; SATURN-2 研究中分别为51.8% vs 14.6% [464].最常见不良反应为滴药部位刺痛灼烧感, 发生率为10%, 随访一年时< 2%患者出现睑板腺囊肿/麦粒肿和点状角膜炎[464,536,537].洛替拉纳滴眼液对于减少无症状患者袖套样分泌物的临床意义仍有待探讨.

秋葵 (Abelmoschus esculentus) 制剂. 秋葵富含多糖及其他具有抗菌和抗炎特性的活性成分[538].鉴于部分TTO眼睑清洁湿巾可能产生刺激性[539,540], 且研究证实TTO衍生物对睑板腺上皮和角膜组织具有毒性[541,542], 临床需要寻找治疗蠕形螨性睑缘炎的替代方案.一项随机对照研究比较了基于秋葵与TTO眼睑清洁湿巾抗螨3个月的效果[543].两组螨虫计数在1个月和3个月时均有所下降, 但秋葵组在两个时间点的角膜染色改善均优于 TTO 组.基于秋葵湿巾耐受性良好, 尚无不良事件报告, 使其可能成为儿童及老年等敏感人群的治疗选择.未来需开展更长期的研究评估基于秋葵清洁产品的抗螨效果.

茶树油. 茶树油(或4-松油醇)是从澳大利亚本土植物互叶白千层的叶片中提取的天然精油, 一直是治疗蠕形螨睑缘炎最广泛使用的传统局部抗菌疗法[505,514].茶树油可以多种形式存在, 包括湿巾,泡沫洁面乳和液体制剂, 它具有抗菌,抗真菌和抗炎特性[544].研究表明, 茶树油浓度在2.5%至50%范围内可有效除螨, 并显著改善睑缘炎的体征和症状[459,509,520,543,545–553].两项研究报告显示, 患者对含2.5%茶树油的眼部清洁湿巾表现出良好的耐受

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性[553,554].虽然茶树油比其他常规家庭疗法(如婴儿洗发水)更能有效杀灭螨虫[551,552], 但较高浓度或长期使用的安全性与耐受性仍需进一步研究[11,12,540].

研究表明, 虽然高浓度茶树油产品(> 50%)比低浓度产品更能有效杀灭螨虫[555], 但> 50%的浓度不适合家庭使用[509].一项体外实验显示, 茶树油对人睑板腺上皮细胞具有毒性, 其毒性浓度甚至比杀灭蠕形螨所需的浓度低10至100倍[541].为此, 新一代配方正在研究中, 其中一种将5% 4-松油醇(T4O)封装在纳米脂质颗粒乳剂中, 在体外作用137分钟内可实现100%杀灭率[556].

睑缘去角质术

目前已有类似电动牙刷的旋转机械装置可用于辅助清洁睑缘和睫毛根部(该过程称为微海绵睑缘去角质术或睑缘去角质术).研究表明, 使用泡沫清洁剂单次治疗即可降低有症状的隐形眼镜配戴者的眼睑细菌负荷, 并改善舒适度和眼表体征[557,558].另外, 使用非电动眼睑清洁刷一个月的效果优于单纯用水清洁, 若与眼部清洁剂联合使用则效果更佳[559].

微海绵睑缘去屑术与茶树油产品联合治疗蠕形螨性睑缘炎有诸多益处.一项 RCT 研究比较了微海绵睑缘去屑术后使用含 T40 眼睑湿巾或安慰剂每日两次治疗一个月的效果, 结果显示蠕形螨感染水平降低, 但两组间在其他干眼病和睑缘炎指标的改善上无明显统计学意义[560].另一项 RCT 比较了夜间使用茶树油洗涤剂和商用眼睑清洗剂联合或不联合微海绵睑缘去屑术的治疗效果, 发现三种方法在治疗2周和4周后对减少毛囊蠕形螨的效果相似[546].一项为期8周的 RCT 研究显示, 治疗前进行微海绵睑缘去屑术预处理, 然后每日2次使用2%茶树油洗剂, 可更有效缓解症状和减少蠕形螨数量[459].因此, 该方法的疗效可能需要超过1个月时间才能显现.目前尚未明确蠕形螨计数减少与干眼症状体征改善之间的直接关联.考虑到长期使用含茶树油产品可能带来的眼表和附属器的不良反应, 建议谨慎使用[11].

对于是否有必要使用微海绵睑缘去屑术等机械干预治疗蠕形螨性睑缘炎, 专家小组(由12名临床医生组成)并未达成共识.虽然该小组中有10人(83%)仍使用此类干预措施, 但他们期望未来出现更有效的治疗药物, 不再需要机械干预[561].

次氯酸

次氯酸是一种强效抗菌剂[563], 具有广谱抗菌活性[562].0.01%浓度的次氯酸在降低睑缘细菌负荷方面与5%聚维酮碘效果相当, 均可减少90%以上的细菌数量, 且不会改变下睑皮肤细菌多样性[564,565].体外实验显示, 0.01%浓度的次氯酸可消除或减少生物膜中的细菌, 但不会破坏生物膜结构, 且对分离出的不同葡萄球菌株的敏感性存在种间差异[566].0.01%浓度的次氯酸具有良好的眼部安全性[539,567], 在多种眼睑清洁剂中可能给患者提供最佳的舒适度[539].

市售次氯酸产品主要为喷雾剂, 浓度范围0.0085%-0.2%.需要进一步研究确定浓度是否与睑缘炎治疗效果相关.次氯酸暴露于光线,空气或极端温度时会变得不稳定, 因此需要加强对患者的健康宣教[568].

相比含HA的湿巾, 使用含次氯酸溶液的湿巾在改善症状(OSDI评分)和眼表体征(泪膜稳定性,泪河高度和睑板腺分泌能力)方面更为有效[457].但治疗一个月后, 两组在 Schirmer 试验,睑板腺成像,角膜染色和结膜充血方面未见差异.眼睑拭子培养显示两组细菌负荷均显著降低, 其中次氯酸组的降低更为明显[457].

一项为期两周的 RCT 研究采用超声雾化给药方式, 发现次氯酸溶液在改善干眼病体征方面优于0.9%生理盐水擦洗眼睑[569], 但由于受试者同时接受每日两次热敷和每日三次0.5%左氧氟沙星滴眼液治疗, 该结果可能受其影响.另一项研究表明, 0.01%次氯酸能缩短蠕形螨存活时间, 改善眼部参数 (Schirmer 试验, TBUT ,角膜/结膜染色)并减轻炎症反应 (MMP-9 和IL-2表达量)[570].

眼睑清洁产品

自 TFOS DEWS II 《管理与治疗报告》[2]发布以来, 多项关于使用眼睑清洁产品治疗前部睑缘炎的临床试验相继发表.睑缘清洁产品最早以湿巾为主, 目前有多种形式, 包括湿巾,凝胶,泡沫,溶液,悬浮液和喷雾剂[571].这些产品均能有效改善干眼病的体征和症状, 且比常用的稀释婴儿洗发水对眼表的不良影响更小, 但目前关于不同产品间的比较研究较少 (表 6).

眼睑清洁产品可分为含抗菌成分和不含抗菌成分两类.抗菌成分包括茶树油,T4O,辛酰甘氨酸,秋葵,次氯酸,芳樟醇和芦荟等, 这些成分近期已有综述进行总结[12].该综述还强调需要在以下方面开展更多研究, 包括产品间对比,标准化的眼睑清洁方法,了解眼睑清洁对患者生活方式的影响(依从性取决于治疗持续时间或症状,成本,易用性,舒适度等), 以及由于各地法规对成分报告要求不同导致的产品比较困难[12].针对眼睑清洁建议方面, 不同眼科专业人员存在差异.一项针对1,139名眼科专业人员的国际调查显示, 推荐患者使用抗蠕形螨眼睑清洁湿巾的从业者数量是推荐在诊所内进行抗蠕形螨治疗的1.55倍[572].最近一项针对261名来自印度和澳大利亚眼科专业人员的在线调查研究了蠕形螨睑缘炎的治疗方法[573].结果显示两个地区的从业者在诊断方法(感知患病率,使用裂隙灯放大识别螨虫)和治疗选择(澳大利亚使用茶树油, 印度使用标准眼睑清洁和热敷),治疗持续时间(澳大利亚更长)和治疗频率(印度:每日2次 vs 澳大利亚:每日1次)方面存在显著差异[573].这些实践模式的差异可能受到法规限制,产品地域可获得性,成本等因素的影响, 但也进一步强调了使用循证方法治疗所有类型睑缘炎的重要性.关于使用热敷治疗MGD 及其疗效的扩展总结可参考一篇关于新型水力加热眼罩的文献[243].

低强度光疗法(LLLT:蓝光)

虽然已知红光和近红外光的LLLT通过光生物调节发挥作用(参见第6.3.1.2.3节), 但相同临床设备发出的蓝光具有不同特性.波长为410-430nm的蓝光具有抗菌特性, 其机制是通过与微生物细胞相互作用产生ROS, 破坏脱氧核糖核酸,蛋白质和脂质等细胞组分, 导致细菌死亡[579,580].蓝光还能影响细菌代谢和应激反应相关特定基因的表达, 例如在骨肉瘤细胞中, 蓝光照射可通过增加ROS水平,调节SOCS3和PTEN/PI3K/AKT等通路诱导细胞凋亡[581].虽然该研究针对癌细胞, 但细菌中可能存在类似机制, 即ROS生成导致细菌损伤和死亡.

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表 **6.** 不同眼睑清洁方法治疗前部睑缘炎的临床试验研究

研究	受试者类型	治疗方案	对照产品	样本量	研究时长	随机对照	显示改善的指标	与对照组无显著差异的指标
Peral等, 2016 [574]	术前患者	辛酰甘氨酸睑缘擦拭巾	无	45	5天	N/A	微生物负荷降低	N/A
Stroman等, 2017 [564]	睑缘炎患者	0.01%次氯酸	无	36(71眼)	20分钟	N/A	细菌分离数减少(尤其葡萄球菌)	N/A
Sung等, 2018 [458]	前部睑缘炎	眼睑清洁泡沫(bid)	稀释婴儿洗发水(bid)	43	4周	是	部分症状,LLT,下睑缘擦伤,圆柱状分泌物,MMP-9表达;婴儿洗发水组MG开口和MUC5AC表达恶化	部分症状,睫毛结痂,倒睫
Eom等, 2020 [575]	白内障术前伴前部睑缘炎及阻塞性 MGD	眼睑清洁组(bid)	无	69	术前3天至术后4周	是	症状,前部睑缘炎,术后1周MG分泌能力,术后1周碎屑&红肿	MG分泌物,MG面积,毛细血管扩张,角膜结膜荧光素染色
Liu和Gong等, 2021 [543]	蠕形螨性睑缘炎	基于秋葵的清洁剂	茶树油	52	3个月	是	蠕形螨存活时间, OSDI ,蠕形螨计数	OSDI,蠕形螨计数, TBUT ,睑酯质量,MG分泌能力
Zarei-Ghanavati等, 2021 [576]	MGD	茶树油洗发剂	常规眼睑洗发剂	40(对侧眼)	4周和12周	是	症状,MG开口堵塞/覆盖,泡沫状泪液,MG分泌能力, TBUT ,毛细血管扩张	睑酯质量,结膜充血,角膜结膜染色, Schirmer 试验,倒睫/双行睫
Arici等, 2022 [545]	脂溢性睑缘炎	睑缘清洁(T4O+透明质酸钠)(bid)	婴儿洗发水(bid)	48	8周治疗+4周随访	是	部分症状	部分症状,NIBUT, TBUT , Schirmer 试验
Runda等, 2022 [577]	MGD	睑缘清洁(bid)+抗生素(qid/bid)和润滑剂(qid)重度 MGD 加用全身抗生素(bid)	湿毛巾+眼睑按摩(bid)+抗生素qid/bid和润滑剂qid+重度 MGD 加用全身抗生素(bid)	50	3个月	是	-	荧光素角膜结膜染色,蠕形螨计数,MG面积
Aghaei等, 2023 [578]	前部睑缘炎	2%茶树油凝胶(bid)	夜间红霉素眼膏+0.01%氟米龙滴眼液(tid)+热敷(bid)+婴儿洗发水(bid)	61	45天	是	症状(第45天),睫毛碎屑,红斑水肿(第45天)	N/A

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此外, 蓝光照射可改变微生物组的组成.一项牙周炎小鼠模型的研究表明, 蓝光照射显著改变了口腔微生物组构成, 降低了α多样性及观测特征数量, 并改变了特定细菌门和属的相对丰度[579].这表明蓝光能选择性影响不同细菌种群, 可能在减少致病菌的同时允许有益菌生长.另外一项针对幽门螺杆菌的体外实验证实蓝光无需光敏剂即可直接杀灭细菌[582].当与光敏剂联用时, 蓝光能增强ROS产生, 从而实现更有效的杀菌效果.这种称为抗菌光动力疗法(aPDT), 已被用于治疗牙菌斑细菌和其他微生物感染[583].

综上, 可能从蓝光LLLT中获益的患者群体主要为睑缘及睫毛细菌负荷过高的患者.通过蓝光LLLT的抗菌特性, 减少睑缘生物膜, 理论上可加速睑缘炎的痊愈进程.目前仍需进一步研究以优化临床治疗方案, 实现睑缘细菌生物膜的有效清除.

麦卢卡蜂蜜

天然蜂蜜因其低pH值,高渗透压,过氧化氢及甲基乙二醛含量, 长期被认为具有抗炎和抗菌特性[584].眼科常研究的为新西兰的麦卢卡蜂蜜(Leptospermum scoparium), 其甲基乙二醛浓度高于其他蜂蜜[585,586].当与α-环糊精复合后, 麦卢卡蜂蜜的抗菌效果可进一步增强[587,588].α-环糊精的环状结构由六个吡喃葡萄糖单元组成, 可容纳亲脂分子的疏水空腔, 能形成水溶性包合物, 从而提高疏水性药物的稳定性和溶解度[589].研究显示, 复合环糊精的麦卢卡蜂蜜体外抗寄生虫效果与50% 茶树油相当[590].

另一项研究调查了53例睑缘炎患者连续三个月每晚在一侧眼睑上涂抹含麦卢卡蜂蜜眼霜(α-环糊精微乳复合制剂)的疗效[591], 结果显示治疗眼从第一个月开始 SANDE 和 SPEED 症状评分显著降低, 三个月时NIBUT,LLT及下睑的眼睑刷上皮病变也改善明显.治疗三个月后, 治疗眼中的眼部蠕形螨,麦氏棒状杆菌,痤疮丙酸杆菌和表皮葡萄球菌负荷均显著减少.最初两周内, 5例患者(9%)因产品涂抹过于靠近睫毛缘或用量过多导致产品渗入眼表, 出现暂时性刺痛和不适.除此之外, 在研究时间内未报告其他严重不良事件, 且患者视力保持稳定[591].由于低pH值可能导致眼表刺激, 目前仍需 RCT 研究进一步验证麦卢卡蜂蜜的疗效和安全性.

局部抗生素治疗

研究表明, MGD和睑缘炎患者的眼睑细菌数量显著增加[167,592,593], 这为抗生素治疗提供了理论依据.口服抗生素在 MGD 治疗中显示出潜力(参见第9.1和9.2节), 局部抗菌剂也可通过不同程度的抗菌活性减少睑缘的微生物数量, 但局部使用抗生素治疗眼睑疾病的研究较少.主要包括红霉素,万古霉素,阿奇霉素,氯己定,次氯酸(详见第7.2.3节),互生叶白千层叶油或茶树油(详见第7.2.1.4节)[592,594].

抗生素耐药可影响治疗效果, 是眼科临床持续关注的问题.ARMOR(眼科微生物抗生素耐药性)监管研究定期报告多种眼部抗生素对结膜分离菌株的最低抑菌浓度[595].研究发现, 抗生素耐药性随着年龄增长而增加, 尤其是针对葡萄球菌属.耐甲氧西林葡萄球菌比甲氧西林敏感菌株表现出更高的多重耐药性(>74%)[595].

阿奇霉素是一种大环内酯类抗生素, 对革兰阴性微生物敏感[596], 同时还具有抗炎特性[597,598].在一项针对睑缘炎和 MGD 患者的研究中, 使用阿奇霉素治疗14天可显著降低细菌负荷, 并改善睑缘血管化,睑板腺开口堵塞和睑酯质量, 且在治疗后两周也未出现不良反应[599].为评估阿奇霉素的长期有效性, 一项针对 MGD 患者的前瞻性观察性队列研究显示, 使用阿奇霉素每日两次治疗两周, 随后每日一次再治疗两周后, 患者的干眼病体征(TBUT, MGD 分级)和症状(畏光,异物感,灼烧感,视力模糊)均有所改善[600].在一年的问卷报告随访中, 患者症状减轻,自我护理治疗(眼睑清洁,人工泪液使用)减少, 生活质量(阅读,夜间驾驶,电脑使用等)提高.

一项研究比较了阿奇霉素滴眼液(15 mg/g, 前三天每日两次, 随后每日一次, 总疗程一个月)与口服阿奇霉素(第一天500 mg, 随后四天250 mg, 共三个治疗周期, 每个周期间隔五天)的疗效[601].结果显示, 局部和口服阿奇霉素均能有效改善临床体征和症状, 且局部治疗在细胞学结果和 TBUT 改善方面更优.另外一项 RCT 试验比较了局部阿奇霉素(15 mg/g, 前两日每日两次, 随后26日每日一次)与多西环素(100 mg每日两次, 持续六周)的疗效[266].结果显示两种治疗均能改善眼表疾病的体征和症状, 组间无显著差异, 但多西环素组的全身副作用发生率更高.

抗炎药物治疗

• 糖皮质激素治疗: 糖皮质激素可有效治疗某些类型干眼病中的炎症和疼痛. TFOS DEWS II《管理与治疗报告》回顾了大量关于使用不同糖皮质激素制剂改善干眼症状和体征的研究[2].该报告同时指出长期使用糖皮质激素可能带来并发症(如眼压升高和白内障), 即使是使用眼部并发症风险较低的氟米龙和氯替泼诺(参见8.1.1节)也需注意. TFOS DEWS II《管理与治疗报告》将局部糖皮质激素纳入分阶段管理和治疗建议的第二步, 并特别强调需要"限制使用时间"和定期复查[2].

自 TFOS DEWS II《管理与治疗报告》发布以来[2], 已有多项关于糖皮质激素治疗干眼病的研究发表[602–604].其中一项系统综述纳入了全球22项 RCT 共4169名受试者, 该报告指出局部糖皮质激素可有效缓解症状,降低角膜染色评分,轻度延长 TBUT, 但对泪液渗透压影响甚微[604].

干眼病的亚型分类对局部糖皮质激素的使用选择至关重要.医生应该寻找并解决原发病因, 而不是将激素治疗轻度下游炎症作为"快速解决方案", 这才是更合适,更长期的管理方法.

0.25%氯替泼诺滴眼液

0.25%氯替泼诺眼用混悬液(Eyesuvis®;Alcon公司, 美国)是目前唯一获得FDA批准用于短期(最长两周)治疗"干眼病急性发作"的酯类局部糖皮质激素, 相较于酮类糖皮质激素, 该药物可将眼组织中的细胞酯酶快速代谢为无活性代谢物, 能减少局部糖皮质激素的典型副作用, 同时保持强效抗炎特性[605–609].

干眼病是一种慢性疾病, 但有许多患者症状呈现间歇性[610,611]. TFOS DEWS II《定义与分类报告》描述了干眼病发展早期出现间歇性症状[612].即使在干眼病病程后

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期, 环境压力(如干燥或多风环境,角膜接触镜佩戴,环境过敏原),眼科手术,局部防腐剂等药物因素及其他原因也可能诱发症状的间歇性发作[613].一项纳入22项研究的Meta 分析表明干眼病存在间歇性"急性发作", 并确定了常见诱发因素, 证实暴露于此类诱发因素的干眼病患者泪液中存在炎症细胞因子[614–617].

药物递送至眼表受到多种因素限制, 包括泪液冲刷,淋巴和血液循环的清除作用, 以及药物穿透泪膜亲水性黏蛋白层的挑战[618].分子要通过黏蛋白层必须具有小分子量,亲水性和中性电荷以避免粘附[619]. 黏蛋白穿透颗粒技术正在开发中[620,621], 与聚合物纳米颗粒相比, 此类颗粒可以制备成即用型水混悬液形式, 提供更好的物理和化学稳定性[622].

有研究报告称, 与传统制剂相比, 黏蛋白穿透型氯替泼诺载药颗粒在兔模型中的角膜递送浓度提高了3.6倍[623].这些临床前研究推动了Eyesuvis用于治疗2800名间歇性干眼病受试者的开发项目[624].自该药物获批以来, 多项研究报道了Eyesuvis治疗干眼病急性发作的疗效和安全性[618,625,626].目前, 其在干眼病等慢性疾病治疗中的应用范围尚不明确, 特别是尚未明确定义干眼病急性发作的缓解标准, 也未确定每年适合使用Eyesuvis的治疗次数.使情况更为复杂的是, 许多更易获得的局部糖皮质激素替代药物并未被专门批准用于干眼病治疗, 且长期使用可带来副作用.

载药人工泪液

载药人工泪液是指以润滑性聚合物为主要成分, 同时添加低浓度活性药物成分作为辅助剂的制剂.这类产品的潜在优势在于能提供更具针对性的治疗, 例如添加糖皮质激素可特异性阻断炎症通路.一项包含38名干眼病患者的随机研究比较了0.2%透明质酸+0.001%氢化可的松与0.15%透明质酸+3%海藻糖两种制剂(均每日四次使用三个月)的效果[627], 得到的结论为两组均能改善干眼症状, 但含药人工泪液组在TBUT 和LLT方面改善更显著[627].另一项针对155名干眼病患者的回顾性研究显示, 与不含激素的人工泪液相比, 含有相同配方的载药组(0.2%透明质酸+0.001%氢化可的松, Idroflog®, 意大利Alfa Intes公司)在45天内能改善 TBUT, 尤其对白内障术后患者效果更明显[628].

使用此类治疗方案时需考虑患者使用时长及潜在副作用风险, 包括含糖皮质激素人工泪液可能导致眼压升高的风险.然而, 在上述为期三个月的对照研究中, 含激素的复方制剂未显著升高眼压[627].

- 局部T细胞免疫调节药物:

环孢素A

环孢素A (CsA)是一种免疫调节剂[629,630], 自2002年Restasis(CsA 0.05%)获得FDA批准以来, 全球已有多种不同剂型的CsA产品获批用于干眼病患者[631].作为钙调神经磷酸酶抑制剂, CsA通过阻断T细胞浸润,活化和炎症细胞因子的释放发挥其免疫调节的作用[630,632–635].

自 TFOS DEWS II《管理与治疗报告》[2]发布后, 在已发表的600余篇关于CsA治疗干眼病的研究论文中, 仅有约60篇为 RCT 研究.这些研究主要关注改进制剂配方以实现更快速的疗效, 并证明其相较于其他干眼病症疗法的优势.最新的一项系统综述和 Meta 分析中纳入了583项使用不同CsA制剂治疗干眼病患者的 RCT 研究 [636].其中30项试验结果显示, 无论剂量或浓度, CsA均有显著的疗效, 另有13项试验结果显示CsA效果与人工泪液,溶剂对照,0.1%氟米龙,0.03%他克莫司或3%地夸磷索效果相当.

CsA的高分子量和疏水性, 加上眨眼和泪液的持续冲刷, 使得现有制剂的药物递送面临挑战[631].目前市售的大多数CsA制剂为含有油类和表面活性剂(如氯化十六烷基吡啶,聚山梨酯80,辛苯昔醇-40等)的乳剂或纳米乳剂.

两项相关研究的合并数据显示, 与溶剂组相比, 对于中重度干眼病患者, 经过6个月0.1%阳离子型CsA乳剂(Ikervis®, 日本参天)的治疗, 角膜染色和症状均有明显改善, 但对干燥综合征患者无效[637].一项针对现有商业CsA制剂的系统综述表明, 不同制剂在改善各类体征和症状方面存在差异[638].

0.05%CsA纳米乳制剂(Cycloome®, 沈阳兴齐, 中国)采用Ailic-Tech®技术制成透明微乳, 可最大限度降低眼部不耐受反应.一项III期研究显示, 治疗组的眼表检测结果从第7天起显著改善[639].在另一项研究中, 该药物在3个月和6个月时改善 Schirmer 评分,角膜杯状细胞密度以及降低树突状细胞密度方面比0.1%氟米龙更有效[640].该制剂还在各种屈光手术后对 OSDI , TBUT ,角膜荧光素染色和改善角膜敏感性表现出显著效果[641–643].

基于半氟化烷烃的无水0.1%CsA制剂是将CsA溶于全氟丁基戊烷, 已在美国(Vevye™;Harrow, 美国)和欧盟(Vevizye®;Laboratoires Thea, 法国)获批.相比其他0.05%和0.1%CsA乳剂, 该产品的扩散性和滞留性可提高局部生物利用度.动物实验表明全氟丁基戊烷能改善脂质层分级, 可能有助于减少泪液蒸发[136,648,649].该产品通过4项 RCT 和1项开放试验长期研究, 共对1500余名干眼病患者进行安全性评估[644–647,650].II期临床研究显示该产品起效快, 且相比0.05%CsA乳剂活性对照组, 眼表染色改善更显著[647].后续3项以水液缺乏型干眼病为主的III期研究均达到主要观察终点, 治疗4周后角膜荧光素染色和结膜染色均较安慰剂显著改善.虽然所有试验中症状较基线均有改善, 但未能一致证明其疗效优于安慰剂[644–646].所有研究中治疗组与安慰剂组不良事件发生率相当;最常见的眼部不良事件为滴注部位反应, 发生率<10%, 低于其他干眼病药物治疗的报道[645,646,651].

研究显示0.09% CsA胶束纳米颗粒制剂(OTX-101;CEQUA®;美国)可有效改善水液缺乏型干眼病患者症状[652–655], 并表现出良好安全性[646].相比于0.15%透明质酸人工泪液, 0.05%CsA纳米乳(Cyporin N®;韩国Taejoon制药)可更有效地改善干眼病患者泪膜稳定性和 Schirmer 试验结果[656].另一项针对干燥综合征患者研究发现, 0.05%纳米乳(Cyporin N)在结膜染色评分方面优于0.05%乳剂(Restasis), 在泪膜稳定性和泪液量方面优于3%地夸磷索[657,658].另有研究比较了CsA乳剂与纳米乳剂的效果, 发现两种治疗均能改善干眼病体征和症状且效果相当[659,660].

一项系统综述纳入了11项比较CsA与人工泪液治疗干眼病的 RCT 研究[661].对1,085名受试者的汇总分析显

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示, 与人工泪液相比, CsA能更显著改善TBUT ,荧光素染色评分, 并使 OSDI 评分平均降低约5分;虽然CsA组报告的不良事件更多, 但均为非严重事件[661].部分研究发现CsA乳剂相比含透明质酸(0.1%,0.15%和0.3%)的人工泪液并无优势[662].然而 0.05% 环孢素 A 纳米乳剂(Cycloome®, 沈阳兴齐, 中国)与安慰剂相比 OSDI 评分有所改善[639], 而对于阻塞型 MGD 患者, 0.05%CsA纳米乳(Cyporin N)的疗效优于0.15%HA联合热敷治疗[663].一项研究纳入中重度干眼病年轻患者, 发现0.15% HA,0.05%CsA(Cyporin N)和3%地夸磷索钠在改善干眼病体征方面效果相当, 但治疗12周后CsA组的炎症标志物下降幅度大于HA治疗组[664].由于多数研究仅持续2-4个月, 最长仅12个月, 因此CsA长期治疗效果尚不明确.

关于人工泪液是否能增强CsA在降低炎症标志物,角膜染色和症状方面的效果, 现有数据并不一致[651,661,665,666].在其他联合治疗方案中, 0.1%CsA联合0.2%氯替泼诺相比单用0.05%CsA在4周随访期内除高阶像差外未见其他优势, 但文献中未明确说明这些指标的评估方法和时间点[667].相比单用CsA, 0.1%CsA联合3%地夸磷索钠能改善 TBUT, 但对症状及角膜结膜染色评分无额外改善[668].

一项 RCT 显示, 在3个月治疗期内, 提高CsA浓度(从0.05%增至0.09%)可改善症状,角膜染色,泪液分泌量和泪膜渗透压, 但对结膜形态和泪膜稳定性无影响, 且报告的不良事件(包括滴药不适感)增加[669].含有3%海藻糖的低剂量CsA(0.01%和0.02%)对重度干眼病患者的疗效与安慰剂相当[670].一项针对62名重度干眼病患者的研究发现, 使用0.1%CsA 治疗6个月或12个月后角膜染色显著改善[671].CsA停药后预估复发时间在接受12个月治疗组为32周, 而6个月治疗组为25周[672].

CsA 在 MGD 治疗领域的研究也取得了一定进展.一项回顾性分析纳入53例 MGD 患者进行为期3个月的研究, 比较0.05%CsA联合无防腐剂透明质酸润滑剂(实验组, 74眼)与单用透明质酸润滑剂(对照组, 32眼)的疗效[673].结果显示, 治疗3个月后, 实验组在 OSDI 评分,TBUT, Schirmer 试验,角膜染色评分,睑缘毛细血管扩张及结膜充血等指标上的改善幅度均显著优于对照组[673].一项前瞻性研究纳入64例干眼病合并 MGD 患者, 将其随机分为三组:第1组(n=24;0.1%HA滴眼液+传统0.05%CsA),第2组(n=21;0.1%HA滴眼液+0.05%CsA纳米乳)和第3组(n=19;单纯0.1%HA滴眼液;对照组)[674].分别在治疗4,8和12周后评估疗效.结果表明:两种CsA制剂均优于单纯润滑剂治疗, 且纳米CsA制剂能比传统CsA更快地改善 MGD 患者的各项干眼病体征和症状[674].

立他司特

5%立他司特滴眼液(Xiidra®;博士伦, 美国)是一种淋巴细胞功能相关抗原-1(LFA-1)拮抗剂.该药物通过特异性结合白细胞表面的整合素LFA-1, 阻断其与配体细胞间粘附分子-1(ICAM-1) 的相互作用, 从而有效抑制T细胞介导的炎症级联反应[675].两项关键III期临床试验 (OPUS-1 和 OPUS-2) 证实, 5%立他司特溶液可改善干眼病的体征和症状[676,677].随后的III期随机多中心临床试验(OPUS 3)也进一步证实了这一点[678]. OPUS 2和OPUS 3共纳入1429名受试者, 分析结果显示在中重度干眼病患者(角膜下方染色评分>1.5且眼干评分>60)中更可能观察到体征和症状的同步改善[679].这一发现为解释 OPUS 1(报告体征改善但症状无改善)与OPUS 2(报告症状改善但体征无改善)研究结果的差异提供了新视角, 因为两项研究纳入的干眼病患者病情严重程度不同.一项纳入 3197 名接受立他司特治疗的干眼病患者的 Meta 分析发现, 该药可改善症状(眼部不适评分,眼干评分,眼部不适评分,OSDI)和体征(总角膜染色评分,鼻侧丽丝胺绿染色评分, TBUT)[680].此外, 基于五项 RCT 共2464名受试者的安全性汇总分析显示, 因治疗相关不良事件导致的停药率为7%.总体而言, 立他司特在干眼病患者中表现出良好的安全性和耐受性[681].

研究还发现, 使用立他司特可减少对人工泪液的依赖[682].一项针对 MGD 患者的 RCT 研究显示, 与热脉冲治疗相比, 立他司特治疗42天后在症状,角膜染色和睑缘红肿方面的改善更显著[683].两项针对白内障手术的干眼病患者的前瞻性研究表明, 立他司特治疗可改善干眼病体征和症状, 并提高生物测量准确性和术后屈光效果[684,685].真实世界研究数据显示, 立他司特使用后眼表症状和体征的改善可持续至停药后12个月[686].

然而, 部分患者报告对治疗存在不满, 主要涉及用药部位刺激感(灼烧感)和味觉异常(用药后出现可能持续4~5小时金属味或咸味)[680,681,687,688].一项系统综述和Meta 分析指出, 16%的受试者出现味觉异常, 其发生率是安慰剂组的36倍[680].

他克莫司

他克莫司 (FK-506) 是一种大环内酯类免疫调节剂, 其作用机制与 CsA 相似, 但以眼膏而非滴眼液形式给药, 且效力强 10-100 倍[689].一项为期6个月的研究直接比较了0.03%他克莫司与0.05%CsA的疗效(每组n=30), 结果显示两种药物均能显著改善患者症状和眼表染色, 减少人工泪液使用频率[690].然而, 在干燥综合征导致的严重干眼病患者中, 两种治疗的疗效差异无统计学意义.另外一项小型 RCT 研究(n=20)证实, 使用0.03%他克莫司眼膏1个月对难治性后部睑缘炎患者具有治疗效果[691].

尽管他克莫司在部分国家已开始使用, 但在全球多数地区仍缺乏商用眼科制剂, 限制了其临床应用.一些研究描述了皮肤用他克莫司制剂的超说明书使用, 证明其对顽固性睑缘炎和干燥综合征患者具有显著疗效[690,691].

- 研发中的药物化合物:

碳化纳米凝胶

碳化纳米凝胶通过盐酸赖氨酸热解形成, 是一种局部用纳米凝胶制剂, 旨在延长眼表滞留时间, 其眼部生物利用度高, 能够实现更长给药间隔和更低给药浓度.兔实验研究结果显示, 其剂量仅为0.05%CsA的十分之一时即能达到相似的治疗效果[692].该纳米凝胶具有自由基清除特性, 并通过其抗氧化和抗炎作用改善眼表健康[692].

非诺贝特

非诺贝特是一种合成过氧化物酶体增殖物激活受体α激动剂, 其通过激活过氧化物酶体增殖物激活受体α, 抑制 Th1 和 Th17 介导的炎症反应[693–695], 同时促进调节

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性T细胞, 降低IL-17和 INF-γ水平[693–695], 不仅对角膜和结膜具有抗炎作用, 还能作用于泪腺.其他研究报道非诺贝特可减轻非肥胖糖尿病小鼠的泪腺炎症,增加水性泪液分泌,减少角膜荧光素染色, 并在高脂饮食实验小鼠模型中部分逆转泪腺的继发改变[693,696].

阿魏酸

阿魏酸是一种从当归根中提取的抗氧化剂, 已在兔模型和体外细胞培养中进行研究.与缓冲盐水对照相比, 该分子能降低TNF-α,IL-6和IL-8等促炎细胞因子水平, 并增加泪液量和改善眼表染色[697].

泪液蛋白

泪液蛋白是一种存在于泪液中的天然糖蛋白, 在干眼病患者中选择性减少[698,699].在Aire小鼠模型中, 局部使用泪液蛋白可改善泪液分泌和角膜染色评分, 并减少泪腺中T细胞浸润, 发挥其治疗作用[700]. Lacripep™ (Tear-Solutions, 美国)是一种合成的含19个氨基酸的泪液蛋白肽段, 保留了完整泪液蛋白单体的生物活性.一项在204名干燥综合征患者中开展的I期临床试验结果显示, 22 μM和44 μM浓度均表现出良好的安全性和耐受性[701].然而在28天研究期结束时, 角膜染色评分和干眼病评分改善尚未达到试验的主要功效目标, 但对于疾病严重程度较高的患者表现出更好的治疗效果.该试验结果提示, 需要进一步考虑患者干眼病严重程度和亚型, 以及剂量滴定以确定未来研究中的最佳方案.

柚皮素

柚皮素是一种天然存在的黄酮类化合物, 广泛分布于番茄,葡萄柚和橙子等水果中.大量研究表明其具有抗氧化,抗炎,抗肿瘤和神经保护等多种生物活性[702].在干眼病小鼠模型中, 柚皮素能改善眼表质量, 表现为泪液分泌量增加以及角膜和结膜染色减少[703].

长效促肾上腺皮质激素注射液

Acthar® Gel(长效促肾上腺皮质激素注射液; Mallinckrodt 制药公司, 美国)是一种天然来源的复合制剂, 含促肾上腺皮质激素类似物及其他垂体肽类成分.该药物通过激活全身多种细胞的黑色素皮质素受体, 兼具类固醇生成和非类固醇生成的免疫调节作用[704].为治疗难治性干眼病, 一项研究对中重度急性干眼病成人患者给予80单位皮下注射(每周两次, 持续12周)[705], 其中15例受试者接受至少1次注射, 12例完成研究.与基线相比, 治疗后第14天和第84天观察到受试者的角膜染色减少, SANDE 评分平均值从62.0逐步下降至46.9, 而 Schirmer 试验结果在整个研究期间未见显著变化.这些结果表明长效促肾上腺皮质激素注射可能是中重度干眼病的有效治疗选择, 但需要更大规模的盲法临床研究加以验证.

瑞普沙拉帕

瑞普沙拉帕 (Aldeyra Therapeutics 公司, 美国)是一种小分子化合物, 可通过与丙二醛和4-羟基-2-壬烯醛竞争生物靶点, 结合活性醛类物质从而抑制炎症反应[706–708].这种结合作用阻止了活性醛类物质与受体和激酶上的氨基及巯基相互作用, 进而阻断涉及NF-κB,炎症小体和其他介质的上游促炎信号级联反应, 减轻Th1和 Th2介导的炎症[706–708].此外, 瑞普沙拉帕还能阻止活性醛类物质与泪液脂质组中的磷脂酰乙醇胺相互作用, 从而避免泪液脂质修饰[708–710].在一项IIa期临床试验中, 51名干眼病患者被随机分成三组, 分别接受瑞普沙拉帕制剂(0.1%滴眼液,0.5%滴眼液和0.5%脂质滴眼液)治疗[708], 结果显示患者的症状和丽丝胺绿染色评分均有改善, 且三组效果相似[708].随后的IIb期多中心试验比较了0.1%和0.25%浓度的瑞普沙拉帕与溶剂对照组的效果, 每组300名受试者, 为期12周[711].结果显示瑞普沙拉帕在改善干眼病患者的症状和体征方面均优于溶剂对照组, 且疗效呈剂量依赖性.基于这些结果, 研究确定0.25%浓度将用于后续III期试验.该药物表现出良好的安全性和耐受性.

局部吡啉制剂

吡啉是一种实验性合成抗氧化剂, 在小鼠和兔模型研究中均观察到局部使用吡啉可改善角膜荧光素染色评分[712,713].

Visomitin

ROS介导的氧化应激被认为在干眼病的发病机制中起重要作用[714].SkQ1是 Visomitin(Mitotech LLC, 俄罗斯)的活性成分, 是一种小分子化合物[715], 可靶向并中和线粒体内天然抗氧化剂无法接触的ROS.在一项随机,双盲,对照的临床研究中, 240例干眼病患者接受Visomitin或安慰剂治疗, 每日三次, 持续六周[716].在第2,4和6周时观察到 TBUT 显著改善, 第6周时中央和全角膜荧光素染色评分显著改善[716].在一项纳入91例轻中度干眼病患者的II期单中心随机对照研究中, 与安慰剂相比, SkQ1在治疗干眼病体征方面显示出疗效, 角膜荧光素染色,结膜丽丝胺绿染色,睑缘充血,眼部不适,干涩感和异物感均有显著改善[717].然而, 随访第29天下方区域角膜染色以及最严重干眼症状的评分无明显改善, 未达到主要疗效终点. Visomitin 在临床试验中显示出良好的安全性和耐受性.

口服抗生素在干眼病治疗中的应用

口服四环素类(四环素,米诺环素或多西环素)或大环内酯类(红霉素和阿奇霉素)抗生素可发挥抗炎作用,降低眼表细菌载量以及改善睑酯质量, 已被用于改善干眼病患者的症状,眼表和泪膜参数.

- 四环素及其类似物: 四环素类是一类广谱抗生素, 对多种微生物具有活性, 包括革兰阳性菌和革兰阴性菌,衣原体,支原体,立克次体以及原虫.四环素类被动扩散进入细菌, 通过抑制30S核糖体亚基干扰蛋白质合成, 阻碍氨酰-tRNA 与 mRNA-核糖体复合物受体位点的结合[718].此类药物能减少产生脂肪分解外酶的细菌[719,720]以及抑制脂肪酶的产生[721], 从而降低睑酯分解产物, 可能有助于改善蒸发过强型干眼病.另外, 还可通过损害胶原酶,磷脂酶A2和几种MMP的活性, 并减少包

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括角膜上皮在内的多种组织中炎症介质(如IL-1和 TNF-α)的产生[722,723], 发挥抗炎特性.

四环素及其类似物已被用于治疗与眼表和泪膜异常相关的疾病, 如酒渣鼻[724],MGD[725,726]以及各种类型的前部睑缘炎[726,727].虽然该领域已有大量研究发表[727], 但迄今为止仅有两项研究采用严格的安慰剂对照和双盲设计.一项 RCT 研究(NCT00560703)比较了口服多西环素(40mg每日一次)与安慰剂治疗3个月在70名前部睑缘炎合并面部酒渣鼻患者中的效果.结果显示多西环素对干眼症状和球结膜充血基本无效. Schirmer 试验测量的泪液分泌量以及 TBUT 测量的泪膜稳定性较基线均有显著改善.另一项 RCT 比较了高剂量(200mg, 每日两次)和低剂量 (20mg, 每日两次)口服多西环素与安慰剂治疗1个月在150例慢性 MGD 患者(每组50例)中的效果.该项研究结果表明, 口服多西环素能适度改善症状, 高剂量组改善更明显, 但组间差异无统计学意义[728].

目前, 口服四环素类药物治疗干眼病的最佳剂量尚未明确.临床通常治疗方案为每日50或 100mg 多西环素(分1~2次服用), 持续数周至数月, 患者耐受性良好.值得注意的是, FDA 目前仅批准40mg/天的多西环素用于治疗玫瑰痤疮(疗程最长16周).这一剂量水平的长期治疗不会导致抗生素耐药性产生, 可能与其抑菌而非杀菌的特性有关[729,730].

四环素类药物可与钙离子结合, 在婴幼儿牙齿发育期使用可能导致牙齿永久性黄褐色改变和釉质发育不全, 同时还会延缓幼儿骨骼生长, 因此在妊娠期和8岁以下儿童中禁用[731,732].长期应用抗生素治疗除胃肠道症状和光敏性等常见副作用外, 还可能增加乳腺癌风险[733,734], 但在一项大规模研究并未证实这一关联[735].目前仍需更多大规模前瞻性研究提供确凿证据.

- 大环内酯类抗生素: 大环内酯类抗生素通过可逆性结合细菌核糖体50S亚基P位点来抑制细菌蛋白质合成以发挥抑菌作用[736].这类药物能在白细胞中主动浓集, 从而被转运至感染部位.用于眼表疾病治疗的主要大环内酯类药物为阿奇霉素和红霉素.口服大环内酯类的耐受性优于四环素类, 且不产生光敏副作用.在使用光能治疗(如IPL)干眼病患者前, 无需提前停用此类药物.

一项关于永生化人睑板腺细胞的临床前研究发现, 给药5天后, 阿奇霉素(而非多西环素,米诺环素或四环素)能显著增加细胞中胆固醇,胆固醇酯,磷脂和溶酶体的蓄积[737].

另外, 一项交叉设计 RCT 研究中纳入115例受试者以比较多西环素(30天总剂量4g;前7天100mg, 每日两次, 后续21天每日100mg)与阿奇霉素的治疗效果(5天总剂量1.25g;首日500mg, 后续4天每日 250mg)[738].根据体征和症状进行方案转换或维持保守治疗.在这项为期9个月的研究中, 两种抗生素治疗 MGD 均有效且安全, 但阿奇霉素具有用药剂量更低,疗程更短的优势(5天vs. 4周)[738].

一项系统综述与 Meta 分析比较了口服阿奇霉素与多西环素治疗 MGD 的疗效[739].该研究表明, 口服阿奇霉素在改善 MGD 体征方面可能优于多西环素, 胃肠道不良事件发生率更低, 但阿奇霉素治疗存在引发严重副作用的风险, 包括心律失常,胰腺炎和眩晕等.由于四环素及其类似物可能导致8岁以下儿童牙釉质异常[731,732], 口服红霉素可作为治疗儿童睑缘角结膜炎的替代选择[740,741].临床通常采用 5mg/kg/天的红霉素口服剂量, 疗程为数周至数月.两项综述指出, 后部睑缘炎或 MGD 相关眼表疾病患者可能在抗生素治疗期间获得短期改善[726,727], 但治疗停止后症状能否持续改善需进一步验证.鉴于长期疗效不明确,常见胃肠道副作用以及可能引发恶性肿瘤等严重全身性问题, 且现有文献不足以证明抗生素在长期 MGD 治疗中具有特殊疗效, 因此这类药物很少被视为一线治疗方案.

眼表再生

- 生物制剂:

血液来源制剂

基于血液成分滴眼液是治疗干眼病的新兴方法, 具有多种制剂类型 (图 1). 这类滴眼液通过提高活性生长因子和介质的浓度, 模拟天然泪液的功能.

自体血清滴眼液

天然泪液是由水,电解质,脂质和黏蛋白组成的复杂混合物, 同时还包含维生素,酶类及1500多种蛋白质[742],细胞因子/趋化因子,生长因子和神经递质[743–745].如 TFOS DEWS II 《管理与治疗报告》[2]所述, 血清中含有多种生长因子: 包括表皮生长因子,神经生长因子 (NGF),转化生长因子-α,角质细胞生长因子,胰岛素样生长因子-1等[746];以及维生素A,E和纤维连接蛋白[747].这些成分被认为能抑制细胞凋亡并促进上皮细胞生长和分化[748,749].

TFOS DEWS II 《管理与治疗报告》[2]回顾了关于血清滴眼液的已发表文献, 引用了14项临床研究, 并将血清滴眼液纳入分阶段治疗方案的第三步.报告指出, 自体血清缺乏业界公认的制备方法,患者获取困难以及污染风险等因素, 限制了该疗法在临床中的广泛应用.目前仅有少数 RCT 研究评估了血清滴眼液治疗干眼病的疗效.究其原因, 或在于此类试验成本高昂, 且缺乏血清滴眼液的商业化生产商.通常, 临床医生多在诊室自行制备血清滴眼液(有时甚至在非无菌条件下操作), 或交由配药药房,采血机构代工, 从而导致制备方法长期缺乏标准化[2].

一项 Cochrane 综述筛选了29项研究, 仅5项符合纳入标准, 指出存在高度异质性和多项结局指标缺乏量化报告的问题[750].其结论认为, 相比人工泪液, 自体血清滴眼液或可短期改善症状, 但需更多 RCT 明确疗效.近期一项对七项 RCT 进行的 Meta 分析报告显示, 血清滴眼液在改善患者症状和多项眼表体征方面优于人工泪液[751].美国眼科学会的一份优选实践评估报告回顾了 10 项研究, 发现其中 8 项质量较高, 表明使用自体血滴眼液可改善症状, 并至少改善一项干眼病的客观临床体征[752].欧洲抗风湿病联盟 (EULAR) 特别工作组提供了一种治疗眼干的路径, 并建议对使用眼部润滑剂和CsA后症状仍未得到控制的患者使用自体血清泪液[753].印度优选实践模式报告指出:现有证据足以支持在

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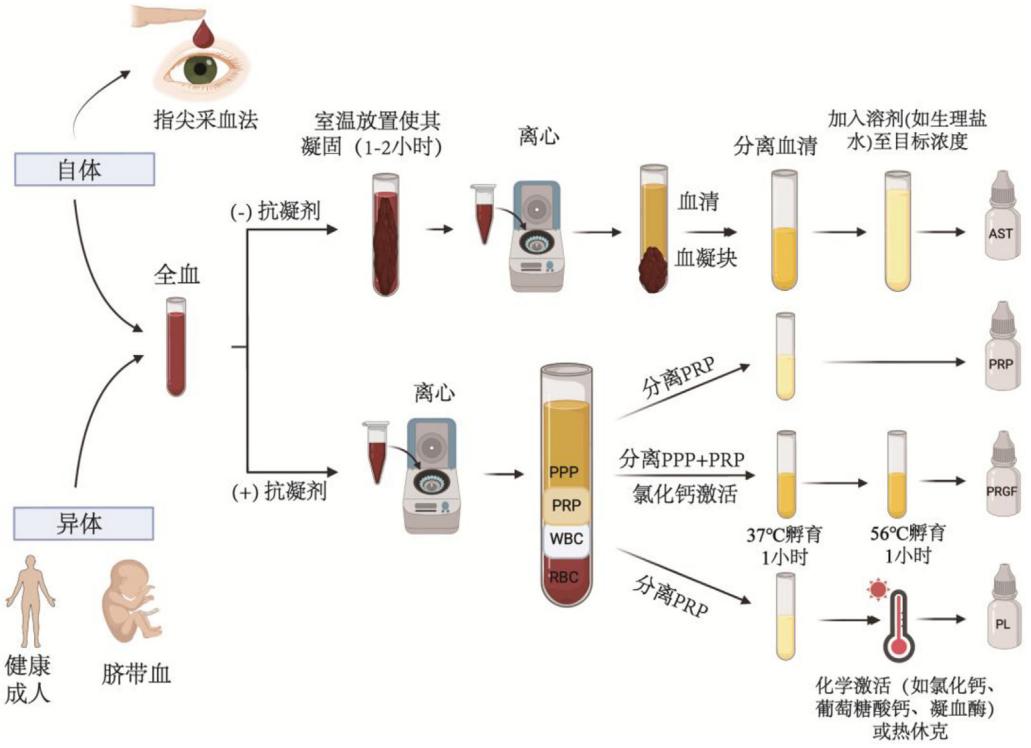

图 1. **自体与同种异体血液来源滴眼液的制备流程.自体泪液来源于患者自身的血液，可以通过指尖采血法(直接应用于眼睛)或全血处理法获得.异体泪液则来源于健康成人供体或脐带血清(UCS)，且仅通过全血处理制备.全血经处理后分为两种路径:无抗凝剂离心制备血清滴眼液，或添加抗凝剂离心分离为贫血小板血浆(PPP),富血小板血浆 (PRP)，白细胞 (WBC) 和红细胞 (RBC). PRP 来源滴眼液可进一步分为: PRP 滴眼液(直接提取),PRGF(富生长因子血浆)滴眼液(PPP+ PRP 经氯化钙激活后56°C孵育1小时)以及PL(血小板裂解液)滴眼液 (PRP 经氯化钙,葡萄糖酸钙,凝血酶化学激活或热休克处理).本图改编自Tovar和Sabater的研究746.**

干眼病患者中使用自体血清滴眼液，但强调其制备方法亟待规范化[754].

尽管无法像常规药物那样规模化生产配送，但值得注意的是，现有机构已采用标准化离心稀释工艺在无菌条件下制备，并通过冷链配送给患者.自 TFOS II《管理治疗报告》[2]发布以来，比较血清滴眼液与FDA批准药物的 RCT 极少.有研究报道指出20%血清滴眼液降低 OSDI 评分的效果显著优于0.05%CsA 滴眼液[755].

同种异体血清滴眼液

自体血清滴眼液的替代方案是使用健康供体的同种异体血清滴眼液.此类滴眼液在特定患者群体中具有优势，例如:静脉通路不良,针头恐惧症,操作不便,认知功能障碍,高龄,行动受限,全身性疾病及血液系统疾病患者[756].一项针对重度干眼病患者的前瞻性随机交叉试验中，一组受试者先接受自体血清滴眼液治疗1个月，随后经过1个月洗脱期后改用同种异体血清滴眼液治疗1个月;另一组则按相反顺序接受治疗.试验结束时两组 OSDI 评分无显著差异，显示两者具有相似的疗效和耐受性[757].一项纳入63名重度干眼病患者的随机临床试验显示:相较自体血清滴眼液，同种异体血清滴眼液与脐带血清(UCS)滴眼液在多项指标上呈现显著性改善，包括: Schirmer 试验，TBUT ,荧光素及丽丝胺绿染色评分等干眼病体征及症状[758]，但组间未见显著差异.对于无法获取自体血清制剂的患者群体，同种异体血清滴眼液似乎是一种安全有效的替代选择.

综上，现有 RCT 证据及高质量 Meta 分析表明，无论是自体还是同种异体制剂，均能快速改善干眼病患者的症状和体征.然而，仍需开展更多 RCT 研究并制定规范的制备指南，以更全面评估其疗效及在重度干眼病治疗中的应用价值.

血小板衍生制剂

血小板衍生制剂与自体血清滴眼液的区别在于，其以血浆作为稀释基质，含有凝血蛋白及血小板源性生物活性成分，如表皮生长因子,转化生长因子-β,血小板衍生生长因子,神经生长因子和胰岛素样生长因子.尽管已有多种富血小板制剂被报道，但其制备通常涉及在不同体积血浆中分离并浓缩血小板，随后激活血小板以释放生长因子.

一项关于血小板源性滴眼液治疗干眼病的系统综述与 Meta 分析纳入了19项针对不同制剂(如富血小板血浆 PRP 与 PRGF) 的前瞻性研究，对比了与人工泪液或自体血清滴眼液的疗效，并评估了治疗前后干眼病的体征与症状[759]. Meta 分析显示，血小板制剂可以改善临床症状和体征(泪液质量,泪液量级角膜染色评分).然而，该研究仅证实 PRP 相较人工泪液可显著改善干眼症状

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与体征, 而 PRP 与自体血清滴眼液在所有干眼病参数上均未显示显著差异.

富血小板血浆 (PRP)

PRP 制剂通过离心经枸橼酸钠抗凝的全血获得血浆分层后提取 PRP 层制备而成, 随后将产物吸出并稀释, 分装至带有滴眼器装置的无菌瓶中备用.

一项纳入368例中重度干眼病患者的研究显示, 患者每日使用 PRP 滴眼液6次,持续6周后, 87.5%的患者 OSDI 评分显示症状改善具有统计学意义, 76.1%的患者角膜染色评分较基线水平显著降低[760].

一项 RCT 研究比较了干燥综合征患者每月接受自体 PRP 泪腺注射联合HA滴眼液(n=15)与单纯使用HA滴眼液(n=15)的疗效[761].治疗90天后, PRP 治疗组所有患者均表现出症状和体征的显著改善, 包括角膜染色评分降低, Schirmer 试验结果增加以及 TBUT 延长, 且未观察到任何不良反应.尽管该研究受限于30例的小样本量, 但其结果表明 PRP 泪腺注射可能成为重症干燥综合征的有效治疗手段[761].

一项纳入44例水液缺乏型干眼病患者的前瞻性,随机,盲法干预研究比较了 PRP 滴眼液(治疗组)与人工泪液(对照组, 39例)治疗30天的效果[762].结果显示, 与对照组相比, PRP 治疗组在治疗15天和30天时均表现出症状,充血程度,泪液渗透压以及角膜结膜染色评分的显著改善, 同时视力,泪液分泌量和杯状细胞密度也显著增加.

一项包含38篇文献的系统综述分析了 PRP 治疗干眼病的疗效[763].多数临床研究报道, 使用人血小板制品(包括 PRP 滴眼液,人血小板裂解液和血小板凝胶)进行治疗后, 患者的体征和症状均有所改善.但由于制备方法和研究设计的差异, 以及术语使用的不一致, 作者建议需要对血小板产品进行标准化表征以实现研究间的有效比较.

一项前瞻性 RCT 研究将38例原发性干燥综合征患者随机分配进行自体血清或 PRP 滴眼液治疗12周[764].两组患者在治疗4周和12周时角膜结膜染色评分和 TBUT 均显著改善, 且组间无显著差异. Schirmer 试验, OSDI 评分,结膜化生分级和杯状细胞密度分级在两组中均未出现显著变化.这些结果表明, 自体血清和 PRP 滴眼液在治疗干燥综合征方面疗效相当.鉴于 PRP 的制备时间较自体血清更短, 作者认为 PRP 可作为干燥综合征患者的一种有效替代治疗方案[764].

富含生长因子血浆(PRGF)

PRGF的制备方法是将血液采集至含枸橼酸钠抗凝剂的试管中, 经离心分离并吸取不含白细胞的血浆层.随后通过添加氯化钙激活血小板以释放生长因子.最终获得的滴眼液富含生长因子,神经营养因子,维生素A和纤维连接蛋白等生物活性介质, 且不含有高水平的促炎分子.虽然制备方法与 PRP 类似, 但 PRGF 被认为是 PRP 的一种亚型, 其特征为富含生长因子,不含白细胞且无促炎活性[765].

一项针对42例 LASIK 术后干眼病患者(共77眼)的纵向回顾性对照描述性研究评估了 PRGF 治疗(38眼, 1-4个疗程, 1个疗程=6周)与对照组(39眼, 每日4次使用人工泪液)的疗效[766].对照组仅在 TBUT 值方面显示出治疗前后的显著变化. PRGF 治疗后, 患者视力, TBUT, OSDI 评分,干眼症状发生频率和严重程度, Schirmer 试验值均出现统计学显著改善, 且未报告任何不良事件.这些结果表明, 与传统干眼病治疗相比, PRGF 滴眼液能有效改善 LASIK 术后患者的干眼症状和体征[766].

在一项首次使用 PRGF 滴眼液治疗不同眼表疾病的多中心回顾性病例系列研究中, 61例干眼病患者通过标准化角膜荧光素染色评分评估的角膜上皮病变以及通过 SANDE 问卷评估的症状, 在治疗后三个月均得到显著改善[767].末次随访时, 74.3%的受试者角膜染色评分较基线水平有所改善, 仅有一例受试者报告了眼部烧灼感这一不良反应.

一项观察性纵向研究比较了59例在标准干眼病治疗方案(包括人工泪液,睑缘清洁和抗炎治疗)基础上加用 PRGF 的受试者, 与43例仅接受标准治疗的受试者在治疗三个月后的疗效[768].结果显示, 与标准治疗组相比, 加用 PRGF 组的 OSDI 和 SANDE 问卷评分,眼部充血程度以及 TBUT 均显著改善, 但两组在角膜染色评分方面未有显著差异.

另一项回顾性研究纳入了83例干眼病患者, 他们在标准干眼病治疗基础上接受 PRGF 滴眼液治疗三个月[769].结果显示 OSDI 症状评分和 Schirmer 试验值较基线水平显著改善.与仅接受标准治疗相比, PRGF 治疗组通过共聚焦显微镜检测的基底膜下神经丛指标也有所改善.

自体血清与 PRP 或 PRGF 的比较

目前鲜有研究直接对比自体血清与 PRP 治疗的疗效差异.一项为期三个月的非随机对照试验纳入22例原发性干燥综合征患者, 比较了100%浓度自体血清制剂与100%浓度 PRP 制剂的治疗效果[770].两组患者的体征和症状均有所改善, 其中自体血清组在视力和 OSDI 评分方面的改善显著更优, 但在角膜染色, TBUT 和 Schirmer 试验方面未观察到显著差异.

一项网络 Meta 分析回顾了39项关于干眼病药物治疗和血液制品治疗的研究(其中>50%为RCT)[771].作者得出血小板裂解液或 PRP 在改善 OSDI 和角膜染色方面优于自体血清, 但由于研究局限性,不一致性和不精确性, 所有配对比较的证据确定性均被评为“低”.

一项单中心,随机,双盲临床试验对96例中重度干眼病患者进行了为期四周的 PRP 滴眼液与自体血清治疗的比较[772].治疗四周后, 两组在 OSDI 评分, TBUT ,眼表染色, Schirmer 试验值,睑酯质量和可挤出性方面均无显著差异[772].

一项研究报道了40例持续性角膜上皮缺损患者(尽管接受了羊膜移植治疗)使用血清滴眼液的效果, 结果显示与人工泪液相比, 血清滴眼液能促进愈合并改善视力恢复[773].

脐带血清(UCS)滴眼液

同种异体 UCS 滴眼液采集自分娩过程中的供体脐带样本, 其表皮生长因子,转化生长因子-β,神经生长因子及P物质浓度均高于自体血清滴眼液[774].UCS可提供促进眼表上皮细胞增殖,迁移和分化的生长因子[775], 这些成分在4°C下可稳定保存1个月, -20°C下可保存3个月[774].

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相较于其他造血血液制品, UCS具有两大优势, 一是单次即可从脐静脉采集大量血清, 无需多次静脉穿刺;二是成本效益更佳, 因脐带血库的监管要求已包含感染筛查, 无需像自体血清供体一样进行额外检测[776].

一项纳入20例患者的前瞻性干预性非对照病例系列研究发现, UCS 使用可增加角膜上皮神经密度, 改善神经形态和角膜敏感性[777].另一项为期2个月的前瞻性病例对照研究比较了 UCS 与自体血清滴眼液对干燥综合征相关和非相关干眼病的疗效[778], 结果显示两种治疗均能延长 TBUT, 且 UCS 在改善眼表染色评分和症状方面显著优于自体血清.然而, 最新一项纳入63例患者,为期3个月的 RCT 研究显示, 自体血清,同种异体血清与 UCS 三种制剂在改善 TBUT ,眼表染色评分和症状评分方面具有相似的临床效果[758].

自体全血滴眼液

近年来, 采用"指尖采血"技术制备自体全血滴眼液治疗干眼病的新方法逐渐受到关注.该技术通过简单的指尖采血方式获取患者少量外周血, 无需特殊处理即可直接用于眼部治疗[779–784].

一项多中心 RCT 研究将60例干眼病患者分为两组:试验组30例在常规治疗基础上加用指尖采血自体全血滴眼液(每日4次), 对照组30例仅接受常规治疗.结果显示, 试验组患者的 OSDI 评分较对照组显著降低, 且治疗过程中未发现明显不良反应[782].另一项包含16例干眼病患者的前瞻性干预性研究也得出了相似结论, 使用自体全血治疗后, 患者的角膜染色评分, TBUT ,视力和眼部舒适指数均有明显改善.但值得注意的是, 在停止治疗 4 周后, 这些改善指标出现不同程度的反复[783].

这种新型治疗方法具有操作简便,成本低廉,无需冷链保存等显著优势, 特别适合在医疗资源相对匮乏的地区推广应用.然而, 其临床应用也面临一定局限性, 主要在于需要患者每日多次进行指尖采血, 这对部分患者的依从性和操作能力提出了较高要求.此外, 关于该疗法的最佳使用频率,长期疗效以及潜在风险等方面仍需更多高质量研究加以验证.

• 润滑素: 润滑素是一种由软骨细胞和滑膜细胞合成并分泌的天然粘液性表面活性糖蛋白(分子量 277kDa), 在维持哺乳动物软骨完整性中起关键作用[785].该蛋白通过覆盖软骨表面提供润滑作用, 同时阻止细胞和蛋白质粘附, 从而降低关节面的剪切应力和软骨降解.目前已有两种与干眼病治疗相关的重组人润滑素制剂被研发.RCT研究显示全长重组人蛋白聚糖(rhPRG4)[786]在0.015%浓度下每日两次使用两周后, 其改善干眼病体征,症状及角膜染色评分的效果优于0.18% HA 人工泪液[787].体外实验证实, rhPRG4 能降低角膜上皮细胞中炎症诱导的细胞因子产生和NF-κB活性, 并可结合 MMP-9 抑制其活性[788].

另一种采用相同细胞系但不同工艺制备的重组人润滑素 (ECF843) 在干眼病临床试验中未显示出优于安慰剂的疗效.分子结构和功能的显著差异可能是造成这两种制剂临床效果迥异的原因[788].润滑素治疗干眼病的有效性仍需更多体内研究验证.

• 羊膜及羊膜提取物滴眼液: 严重干眼病可导致角膜中央或弥漫性,粗糙的上皮微糜烂.这些糜烂可能进一步融合形成上皮缺损, 增加角膜感染或溃疡风险, 最终导致视力丧失.羊膜移植可考虑用于促进角膜上皮愈合并减轻眼表炎症. PROKERA® SLIM (美国Bio-Tissue公司产品)是一种置于单层塑料环内的人羊膜装置, 可像巩膜接触镜一样置于眼表.该膜通常在3-5天内溶解, 但也可在未完全溶解时取出.目前尚未见相关 RCT 研究发表.两项多中心回顾性病历研究报道了对其他治疗(包括自体血清滴眼液和0.05% CsA)无效的严重干眼病患者使用冷冻保存羊膜的结果[789,790].治疗2-7天后, 约2/3至3/4的患者报告症状显著改善, 且三个月随访期眼表染色评分明显下降.约10%的患者在三个月随访期内需要重复治疗才能完全愈合.两项研究均报告了眼部不适的不良事件, 但未提及严重程度或频率.

一项成本效益决策树模型分析显示, 从直接和间接的社会成本角度看, 冷冻保存羊膜一年期的成本效益优于0.05% CsA(成本/效用:18,275美元/0.78 vs 20,740美元/0.74) .但若仅考虑直接成本, 一年期内0.05% CsA是最经济的治疗方案(4,112美元 vs 10,300美元)[791].

另一种治疗选择是采用γ射线灭菌的干燥羊膜联合绷带式角膜接触镜, 这是一种无需缝合,无痛的门诊治疗方式.一项纳入52例患者(56眼)的回顾性研究显示, 经过1-2周治疗后, 患者的角膜上皮糜烂得到改善[792].无论是冷冻保存还是脱水处理的羊膜均呈半透明状态, 多数患者报告存在视力模糊现象.为解决视力相关问题, 可采用包括有 6mm 中央光学区, 大直径 (17mm) 脱水羊膜 (Omnigen® VIEW, 英国 NuVision 公司产品)联合 18mm ,74%含水量的软性绷带镜 (OmniLenz®) .一项前瞻性研究纳入35例中重度干眼病患者, 双眼接受8-10天治疗后, 患者症状改善31%, 眼表染色评分降低42%[190].另一项针对中重度干眼病患者的 RCT 研究表明, 每周两次,持续一周的治疗能快速显著改善干眼症状和眼表体征, 效果可持续至少三个月, 同时能促进角膜神经修复并减少活化/成熟的角膜炎症细胞数量[793].

关于羊膜提取物滴眼液治疗眼表疾病的效果, 一项纳入12项研究的综述显示[794]:在205例患者 (296眼)中, 59%用于干眼病治疗, 23%用于上皮缺损, 其余18%用于其他角膜愈合障碍.提取物制备方式主要包括冻干,匀浆和新鲜羊膜提取三种.所有研究均报告了不同程度的症状和体征改善, 眼部不良反应发生率为2.3%.综述结论认为, 现有证据支持羊膜提取物滴眼液是治疗眼表疾病的有效工具[794].

• 0.002%塞奈吉明: 神经生长因子于20世纪 50 年代首次被发现, 后续研究证实其对角膜和结膜的营养支持,敏感性及愈合过程具有关键作用[796,795,797].0.002%塞奈吉明滴眼液(Oxervate®, 20 μg/mL, 意大利)是一种含重组人神经生长因子的滴眼制剂[798], 目前获 FDA 批准用于治疗神经营养性角膜炎[799].基于其作用机制, 该药物在干眼病治疗中的潜力也正在探索中[800].

两项针对中度(二期)和重度(三期)神经营养性角膜炎患者的 RCT 研究显示, 塞奈吉明治疗组8周后角膜完全愈合率达65%-72%, 显著高于安慰剂对照组的17%-33%[801,802].最常见的不良反应为给药部位疼痛(发生率约16%).另一项研究在40例中重度干眼病患者中评估了

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局部应用人 NGF(20 μg/mL 或4 μg/mL 浓度, 每日两次, 持续28天)的安全性和有效性[800], 但由于缺乏对照组, 研究者认为观察到的症状和体征改善可能至少部分源于安慰剂效应.

• **RGN-259 0.1%:** RGN-259 0.1%(RegeneRx 生物制药公司, 美国) 是一种合成制剂, 其活性成分为天然分子胸腺素β4(Tβ4)的仿生拷贝[803].在干眼病小鼠模型中, 局部应用 RGN-259 可促进角膜上皮细胞迁移,恢复黏蛋白及杯状细胞功能, 并减轻炎症反应[804].

一项III期临床试验显示, 对于二期和三期神经营养性角膜炎患者, 每日五次局部应用该滴眼液可显著提高角膜完全愈合率,加速愈合进程,减小病灶范围及严重程度, 并改善眼部舒适度.该药物表现出良好的安全性和耐受性[803].

• **丝源蛋白 (SDP-4):** 泪膜黏蛋白因其两亲性化学特性可润滑眼表, 同时通过天然生物活性维持眼表微环境稳态[805].丝源蛋白(SDP-4)是从家蚕蚕茧中提取的天然蛋白[806], 其作用类似于黏蛋白, 并可作为潜在毒性较高的润滑剂和表面活性剂的替代品[807].

体外研究证实, 丝源蛋白通过抑制 NF-κB通路调控促炎信号传导[808–810].在干眼病小鼠模型中, 水性丝源蛋白能通过减少炎症因子基因表达及细胞间黏附分子-1,MMP-2和 MMP-9 的分泌, 显著增加泪液分泌,降低角膜不规则性,抑制上皮细胞脱落并提高杯状细胞密度, 从而改善临床症状[811].

首项SDP-4人体临床试验采用双盲,随机,平行组,连续队列设计, 中重度干眼病患者每日两次给药, 持续84天[812].结果显示1% SDP-4滴眼液组患者 TBUT 较基线显著增加, 改善程度显著优于溶媒对照组;虽然症状评分与对照组改善相似, 但超过90%的患者报告用药舒适性良好.

• **局部胰岛素治疗:** 研究表明, 眼表组织[813]及泪腺[814,815]均存在胰岛素受体表达, 且泪液中可检测到胰岛素样生长因子[816,817].2013年一项小规模回顾性研究首次报道了局部胰岛素对眼表疾病的潜在作用:在糖尿病患者的玻璃体视网膜手术中, 相比常规治疗, 局部胰岛素滴眼液能加速术中角膜上皮缺损的愈合, 改善术中对眼底的观察[818].一项纳入 160 例糖尿病相关干眼病患者的临床试验显示, 在为期4周,每日4次的治疗中, 局部胰岛素组与人工泪液组分别有66%和63%的患者症状较基线改善, 但组间无显著差异[819].值得注意的是, 该研究未观察到两组患者在泪膜及眼表参数方面有任何显著改善.

解剖结构异常相关治疗

• **眼表解剖结构异常:** 影响眼表形态学的解剖结构异常可通过造成不规则表面, 阻碍泪液铺展及泪膜的形成与维持, 从而诱发或加重干眼病.

结膜松弛症

结膜松弛症表现为球结膜与睑缘之间出现松弛,冗余的非水肿性下方球结膜.这种与年龄相关的眼表病变虽对生活质量影响显著, 却常被忽视[820,821].与较轻度的结膜皱褶(即睑缘平行结膜皱褶, 参见11.1.2节)类似, 结膜松弛症与干眼病高度相关, 在干眼病患者中报告患病率高达54%[822].

尽管确切病因尚未明确, 其危险因素及相关疾病包括:年龄,女性,角膜接触镜配戴,干眼病,远视,睑裂斑,紫外线暴露及眼睑疾病[821].结膜松弛症引发干眼症状的机制可能与 TMH 降低有关[823,824].此外, 当病变位于鼻侧时, 溢泪是常见症状, 手术矫正通常可缓解此症状[825,826].研究显示, 鼻侧结膜松弛症患者比颞侧或无病变者表现出更严重的干眼症状及体征 (Schirmer 试验值更低,睑板腺缺失更显著,睑缘血管充血更明显)[820,827].

结膜松弛症与 MGD 及睑板腺缺失存在密切关联, 这表明脂质缺乏可能通过减少润滑作用而间接影响疾病进展, 导致结膜组织与眼表之间的摩擦增加和"牵拉"效应[828].另一种假说认为, 结膜松弛症会影响眨眼的完整性, 从而导致睑板腺缺失和继发性脂质缺乏.一项针对39例接受结膜切除术的结膜松弛症患者的研究显示, 术后3个月患者的 OSDI 评分, TBUT ,角膜染色以及泪河面积均有所改善[829].

结膜松弛症的治疗方法包括局部润滑剂,抗炎药物,夜间涂抹眼膏等保守治疗, 以及多种手术干预(详见14.4.1节), 如电灼术,结膜切除术,结膜巩膜固定术,结膜结扎术,激光结膜成形术,射频电凝术和等离子结膜成形术等[830–834].有两篇文献提出了使用射频技术治疗结膜松弛症的方法[834,835], 另外两篇文献则表明基于透明质酸的人工泪液有助于缓解结膜松弛症引起的症状[628,836].

睑缘平行结膜皱褶

睑缘平行结膜皱褶的特征表现为下方鼻侧及颞侧球结膜出现与下睑缘平行的皱褶[837].一项纳入 26 项研究的系统综述显示, 无论是角膜接触镜配戴者还是非配戴者, 睑缘平行结膜皱褶和结膜松弛症均与干眼症状显著相关[833].对于继发于睑缘平行结膜皱褶的干眼病, 治疗主要以规律使用润滑剂为主[833].

睑裂斑

睑裂斑是指睑裂区鼻侧和/或颞侧球结膜发生的纤维脂肪性退行性改变[838].其病因被认为与翼状胬肉形成类似, 与紫外线暴露相关[838].其物理存在同样可能改变眼睑/眼球的对位关系, 从而影响泪液的铺展和功能.与翼状胬肉类似, 手术切除睑裂斑已被发现可减轻干眼病的体征和症状[839], 但这一结论仍待高等级循证医学证据确认.(参见 14.4.2 节).

翼状胬肉

翼状胬肉是一种进行性,翼状纤维血管增生性病变, 通常起源于鼻侧和/或颞侧结膜, 随时间推移向角膜延伸[840].作为全球最常见眼表疾病之一, 其平均患病率达10.2%[841], 主要与高强度紫外线暴露相关[840].翼状胬肉是公认的干眼病危险因素[13], 63.6%的原发性或复发性胬肉患者报告存在干眼症状[842], 包括刺激感,干燥,溢泪

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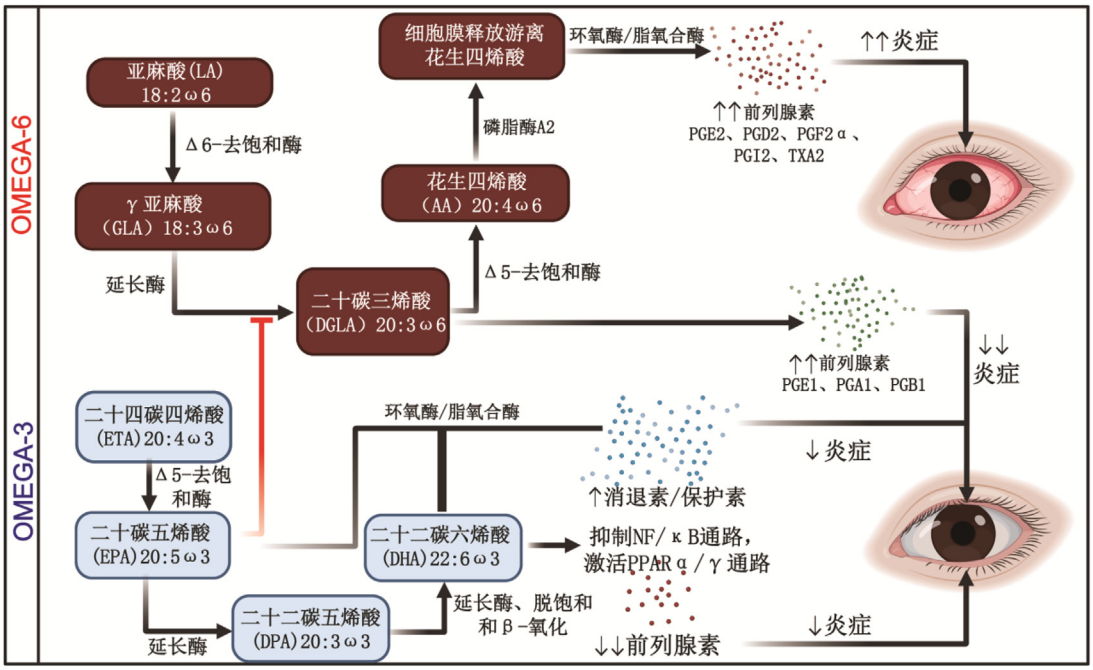

图 2. **ω-6与ω-3脂肪酸的关键代谢途径.短链ω-3和ω-6脂肪酸通过两条独立,共享并竞争同一系列酶的代谢途径转化为长链脂肪酸.总体而言, ω-6途径主要产生促炎介质:亚油酸经过一系列步骤转化为花生四烯酸, 后者进一步代谢为包括多种前列腺素在内的生物活性代谢物.虽然ω-6途径也能产生某些抗炎介质(特别是 PGE1), 但主要生成促炎介质.在ω-3途径中, α-亚麻酸转化为包括二十碳五烯酸 (EPA) 和二十二碳六烯酸 (DHA) 在内的长链脂肪酸, 随后产生各种抗炎介质, 包括消退素和保护素家族.这些物质在干眼病中具有重要意义, 因为它们可以调节上皮细胞存活,氧化应激恢复和伤口愈合等生理过程.ω-6/ω-3比例高的饮食被认为具有促炎作用, 因其倾向于产生促炎介质, 会增加出现干眼病体征和症状的可能性.图中的红线表示对该途径的抑制作用.本图由Rohan Bir Singh(MD)通过BioRender创建(2025年)(https://BioRender.com/n49o832.)**

及异物感[840].胬肉患眼的TBUT显著缩短[843], 与无胬肉对照组相比, 其睑板腺评分,睑缘异常及睑酯评分亦存在显著差异[843,844].胬肉的存在会破坏泪膜正常功能, 而手术切除(参见14.4.2节)通常可有效缓解干眼症状[845].

营养调整与替代疗法

近年来, 饮食调整,营养补充及替代疗法在干眼病治疗中的潜在作用日益受到关注.《 TFOS 生活方式报告:营养对眼表的影响》详细探讨了营养因素与干眼病的关系[16], 其他综述也对这一主题进行了深入分析[18,846,847].

• 宏量营养素: PUFA, 特别是ω-3脂肪酸, 对改善包括干眼病在内的眼表炎症相关临床症状具有关键作用(见图 2). ω-3脂肪酸代谢衍生物(如消退素D1/E1和保护素)可通过抑制白细胞浸润和增强巨噬细胞活性来缓解眼表急性炎症, 从而改善角膜上皮完整性和泪液分泌[16,848–851].其中, 源自二十二碳六烯酸的神经保护素 D1 在抑制眼表炎症和神经保护方面的治疗作用已得到广泛研究[852,853].多种病因导致的角膜神经病理损伤可能引发角膜上皮完整性丧失,创面愈合延迟甚至溃疡形成[854].一项研究表明, ω-3 PUFA 的摄入与角膜神经参数改善相关, 因此补充这类必需脂肪酸可能有益于眼表健康[855].

正如Cochrane系统综述所指出的, PUFAs 在干眼病治疗中的潜在作用仍存在不确定性[856]. DREAM 研究发现, 随机接受含3000 mg ω-3脂肪酸补充剂或5000 mg 橄榄油安慰剂治疗12个月的干眼病患者均有所改善, 但ω-3脂肪酸组并未优于安慰剂组[857,858], 这一结果对 PUFAs 在干眼病治疗中的益处提出了质疑.由于 LTα基因型会影响对ω-3 PUFA的炎症反应, 这应被视为治疗结果的潜在混杂因素, 也可能解释不同研究间的差异[859].

一项多中心临床试验表明, 与安慰剂对照组相比, 每日补充2400 mg ω-3 PUFAs可显著改善干眼症状, Schirmer 试验值, TBUT ,泪液渗透压和结膜杯状细胞密度[860].此外, 一项纳入19项 RCT 的 Meta 分析显示, ω-3 PUFA 膳食补充可显著改善干眼症状和体征[861].另一项针对45-84岁女性的大型横断面研究表明, ω-3脂肪酸摄入量较高者干眼病风险降低, 而ω-6与ω-3 PUFA 摄入比例较高则会导致干眼病风险增加[862].同一作者还发现, 定期食用富含ω-3的金枪鱼可显著降低干眼病风险[862].这些发现表明ω-3 PUFA 对维持眼部健康和预防干眼病具有重要作用, 尽管相关证据仍存在争议[857].

其他植物油和种子, 如特级初榨橄榄油和亚麻籽油, 已被证实对维持眼表健康有积极作用[124,126,863–866].一项研究表明, 口服富含α-亚麻酸的亚麻籽油180天后, 干眼病患者的症状和体征较基线显著改善[866].相比之下,

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棕榈油,玉米油和大豆油中ω-6与ω-3脂肪酸的比例较高,可能促进慢性炎症并对眼表产生不良影响[867].此外,摄入氢化植物油中的反式脂肪酸与全身性炎症相关,可能进一步损害眼表健康[868].

尽管近期有系统综述探讨了局部使用ω-3 PUFA的疗效和潜在应用价值,但目前相关研究数量仍然有限,且此类产品的可获得性较低[869].综合现有证据表明,口服ω-3 PUFA 补充剂可能对干眼病患者具有益处.然而,脂肪酸的最佳来源,剂量及ω-3与ω-6的比例仍需进一步研究确定.

- 微量营养素:维生素(参见6.1.1.10节)和矿物质等微量营养素对维持眼表健康具有关键作用[15,17,846].维生素A对维持免疫功能和眼表上皮完整性至关重要[870,871].其缺乏可导致干眼病和角膜穿孔等严重眼病,是发展中国家儿童盲的主要原因之一[872].在发达国家,胃旁路手术(常用于减重)和酒精中毒是成人维生素 A 缺乏的常见原因[872],此外,严格限制性饮食也可能导致成人和儿童缺乏维生素 A [873–875].

对于维生素A缺乏者,口服补充可能有助于改善干眼病,但其在非缺乏患者中的作用尚不明确[15].短期口服维生素A可改善干眼病患者泪液质量而非分泌量[876],未来研究需扩大样本量并延长干预时间.局部维生素A滴眼液在改善干眼病患者泪膜稳定性和眼表健康方面效果更显著[15,164].

对于 MGD 相关干眼病,维生素A与CsA联合治疗可能更具优势.一项研究显示,与单纯0.1% HA滴眼液联合CsA相比,12周联合维生素A治疗在 TMH , OSDI 评分, Schirmer 试验和 TBUT 方面改善显著[877].

维生素B12对 DNA 合成和神经功能至关重要,其缺乏与干眼病风险增加相关[20].一项纳入30名绝经后女性的研究表明,使用含维生素 B12 ,0.3% HA ,P-plus,氯化钠,氯化钾,氯化钙,氯化镁和稳定复合氯氧化物的滴眼液治疗1个月后,患者眼表疾病参数和干眼症状较基线显著改善[168].另一项研究显示,干燥综合征(伴严重干眼病)患者在接受维生素B12联合含HA滴眼液治疗后,Schirmer 试验值, OSDI 评分,TBUT 和泪液荧光素清除试验均显著改善[878].

维生素D是另一种关键微量营养素,在钙稳态,免疫调节以及细胞增殖和分化中起重要作用[879].一项纳入14项观察性研究的 Meta 分析表明,干眼病患者的血清25-羟基骨化三醇水平显著降低[172].此外,一项包含100名维生素D缺乏者的随机临床试验报告,口服补充维生素 D 持续 8周后,患者的 Schirmer 试验值,TBUT 和泪液渗透压显著改善[880].

硒,锌和铜等矿物质对眼表健康也具有重要作用,其中硒以其抗氧化特性著称[881].硒是泪腺中硒蛋白P生成的必需成分,并存在于泪液中[882].研究表明,干眼病患者硒蛋白P水平显著降低,这可能与眼表氧化损伤有关[882].

- 天然产物与干预措施:

针灸疗法

针灸的治疗效果被认为通过多种机制实现,包括降低干眼病等慢性炎症状态下的促炎细胞因子表达[883–886],同时可增加全身血流灌注,减轻疼痛感知并调节交感神经系统[887–889].多项研究显示,接受针灸治疗的干眼病患者症状和眼表情况显著改善[890–896],但并非所有研究均能复现该结果[897,898].

一项包含假针灸对照组的随机双盲临床试验表明,连续两日针灸治疗可改善干眼症状[883].因未观察到泪液分泌量,TBUT 或眼表染色的改变,该研究提示针灸可能主要通过调节疼痛强度或阈值而非增强泪腺功能发挥作用.一项针对针灸联合人工泪液治疗干眼病的系统综述与 Meta 分析(共纳入16项研究,1383例受试者)证实,该联合疗法在评估干眼病客观指标时安全有效[899].另一项研究表明,与单纯使用人工泪液相比,八次针灸疗程显著改善结膜充血程度[900].

草本植物与香料

草本植物(通常是指生长在温带气候的软茎植物的叶子和茎)对眼部健康具有潜在治疗作用.决明子(豆科)的重要成分大黄素,其抗氧化特性在线粒体脂质过氧化系统中起重要作用.一项 RCT 研究表明,含花青素,虾青素,维生素A,C和 E 及决明子,麦冬等草药提取物的抗氧化剂可通过减少ROS 从而促进泪液分泌和维持泪膜稳定性[901].

另一种草药枸杞含有抗氧化剂玉米黄质,叶黄素及抗炎多糖[902],其有效成分枸杞多糖具有抗炎和抗凋亡作用.动物实验显示,枸杞可通过增加泪液量,延长 TBUT 及减轻角膜结膜荧光素染色改善干眼病[903].

姜黄素是从姜黄中分离的多酚类物质,通过清除活性氮/氧物质发挥抗氧化作用,并具有抗炎特性[904,905].体外研究证实,姜黄素通过p38 MAPK/NF-κB 通路抑制高渗环境诱导的角膜上皮细胞 IL-1β上调[906].

牛膝含皂苷和植物蜕皮激素等多种抗炎分子[907].临床前研究显示,局部应用牛膝提取物可改善角膜表面不规则性,减轻角膜上皮病变并增加结膜杯状细胞密度[697].当归中的阿魏酸及银杏/蜂胶中的山奈酚已被证明能下调人角膜上皮细胞促炎因子 (IL-1B ,IL-6,IL-8, TNF-α)表达[908].

局部应用从中草药"秦皮"中提取的七叶内酯已被证实能够灭活与慢性眼表炎症相关的 ERK1/2 通路.在兔干眼病模型中,该作用可增强CsA的抗炎功效[909].

尽管初步证据显示积极效果,但仍需通过精心设计的临床试验来评估膳食草本植物与香料在眼表疾病中的潜在益处.

水合作用

充足的水分对于维持最佳的身体机能至关重要,包括眼表功能.尽管直接证明水合状态与眼表健康相关性的证据有限,但研究表明血浆渗透压(全身水合水平的标志物)与泪膜渗透压呈直接正相关[910,911].干眼病患者常表现出更高的血浆渗透压,提示脱水可能损害泪腺功能并增加泪液渗透压[912].值得注意的是,荷兰一项纳入51,551人的横断面研究显示,干眼病患者的饮水量反而更高[913].目前尚缺乏关于饮水量对眼表参数影响的临床试验证据.

乳铁蛋白

乳铁蛋白是一种由粘膜上皮细胞产生的铁结合糖蛋白,具有明确的抗炎,抗氧化和抗菌功能[914].既往研究证

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实, 泪液乳铁蛋白水平降低与干眼病显著相关[915–917].口服乳铁蛋白可维持束缚和干燥应激诱发的干眼病小鼠模型中的泪液分泌.据推测, 这种作用是通过肠道菌群调节介导的[918].

干眼病的高渗环境会触发炎症和氧化级联反应, 导致上皮增殖和分化受损[919].乳铁蛋白通过其铁螯合特性提供氧自由基和羟基清除活性[714,920,921], 从而抑制 ROS 的促炎和组织损伤效应.此外, 乳铁蛋白还能通过抑制经典补体激活途径和下调炎症介质来缓解过度炎症反应.

麦卢卡蜂蜜

如第7.2.6节所述, 麦卢卡蜂蜜具有抗菌,抗真菌,抗病毒,抗炎和抗氧化特性[922].多项临床试验表明, 局部应用天然或复合配方的麦卢卡蜂蜜对干眼病[923,924], MGD[925,926],前后睑缘炎[587,591,927]以及接触镜相关干眼病[928]患者具有抗炎和治疗作用.一项纳入5项研究, 323例受试者的 Meta 分析显示, 蜂蜜及其衍生物治疗可显著改善患者 OSDI 评分, 同时改善 Schirmer 试验值和角膜荧光素染色评分[924].

蜂蜜作为膳食补充剂对眼表疾病的治疗作用研究较少.一项 RCT 研究评估了口服蜂王浆(蜜蜂用于喂养蜂王和幼蜂的胶状物质)对干眼病患者的影响, 发现 TBUT 和 Schirmer 试验值显著改善(尤其在基线值较低的患者中), 但干眼症状未见明显缓解[929].

营养补充剂

两项前瞻性随机临床试验评估了含叶黄素,玉米黄质,姜黄素和维生素D的膳食补充剂 (NutriTears®), 结果显示其可显著增加泪液量,提高泪膜稳定性, 并降低泪液中 MMP-9 炎症标志物水平[175,930], 表明通过摄入膳食补充剂可能对干眼病产生临床获益.

手术相关医源性干眼病的预防与治疗

白内障和屈光手术可能诱发或加重干眼病[12,931–933], 导致干眼症状加重和手术满意度降低[934,935].围手术期优化眼表状态可减轻症状并改善临床体征和屈光结果.

• 干眼病与白内障手术: 业界共识认为术前应优化眼表状态[933], 以降低术后屈光误差[936,937],视力波动及眼表相关症状新发或加重的发生率[938].已进行多项前瞻性 RCT, 评估术前使用不同干预措施治疗 MGD 的效果, 包括矢量热脉动[935,939–941],IPL[942]和低强度光疗[351], 总体结果显示治疗组患者的 MGD 主观症状和客观体征较对照组改善.

一项前瞻性,随机,开放,多中心研究评估了矢量热脉动对植入景深延长型IOL患者的影响[939].术后3个月, 术前接受热脉动治疗组的光晕不良反应发生率显著更低, 但多重像或双像的不良影响发生率更高.对照组术后接受热脉动治疗后, 视力和总睑板腺评分显著改善[939].

另一项前瞻性,随机,干预性,对照,双盲临床试验对健康参与者在手术前后一周进行预防性低强度光疗法与 80 名对照组进行了比较[351], 发现治疗组术后1个月低强度光疗组的 OSDI 评分显著更低, 非侵入性泪膜稳定性更高[351].

两项研究评估了术前单独[943]或术前术后联合[575]实施睑缘清洁的益处, 受试者 MGD 主客观指标均改善.针对白内障术后持续超过1个月的干眼病患者的研究显示[944], 含茶树油的睑缘清洁联合人工泪液和激素滴眼液方案, 较不含茶树油的方案在 TBUT , OSDI ,泪液渗透压和蠕形螨数量方面改善更显著, 但两组 Schirmer 试验结果无显著差异.

• 干眼病和屈光手术: 角膜屈光术后早期出现干眼症状较为常见, 通常会在6-12个月内逐渐改善[933,945,946].然而, 仍有少部分患者对常规治疗无反应, 发展为难治性干眼病.研究表明, IPL[328,947],热脉动治疗[948]和热敷[949]等干预手段对激光视力矫正术后难治性干眼病患者具有显著疗效.

两项前瞻性研究针对既往10年内接受过屈光手术,且经过至少1年常规治疗仍持续存在 LASIK 相关难治性干眼病的患者进行了 IPL 疗效评估[328,947].首项研究对 42 眼实施两次 IPL 治疗(间隔2周), 结果显示与对照组(n=30眼)相比, 治疗组的 NIBUT 在第二次治疗后第14天即显著改善, 第28天时 NIBUT , OSDI 评分,泪膜脂质层,睑板腺质量均显著改善[947].第二项研究纳入50例术后超过1年仍存在中重度干眼病的 LASIK 术后难治性干眼病患者, 比较了单纯 IPL 治疗(两次)与 IPL 联合每日热敷眼罩的疗效(两组均每日使用0.1%透明质酸滴眼液), 结果显示两组主观和客观干眼病参数均改善, 且联合治疗组效果更为显著[328], 证实门诊治疗与家庭护理的协同效应.但需注意的是, 这两项研究仅评估了短期(28天)疗效.

一项回顾性研究评估了57例 (109眼) 激光视力矫正术后常规治疗无效的难治性干眼病患者接受矢量热脉动治疗的效果[948].单次治疗后1个月及6-8个月复查时, SPEED II 评分均显著改善, 同时客观检查显示 TBUT 延长,睑板腺通畅性改善,角膜荧光素钠染色减轻.另一项前瞻性开放标签非对照试验中, 37例激光术后2年仍存在持续性干眼病的患者接受20分钟热敷眼罩治疗, 结果显示治疗后5分钟LLT和 TBUT 显著增加[949].

一项双盲临床试验将61例拟行激光视力矫正的健康受试者随机分组: IPL 组(术前,术后1周和3周各1次治疗)与假治疗组[950].3个月随访时 IPL 组 OSDI 评分, NIBUT , TMH 和睑板腺成像较对照组改善, 而对照组 TMH 较基线恶化;至6个月时虽然 OSDI 差异消失, 但NIBUT, TMH 和睑板腺成像的组间差异仍具统计学意义.研究者认为围手术期 IPL 安全有效, 但对接受屈光手术的无症状健康人群的成本效益比提出质疑.另一项前瞻性干预研究显示, 合并 MGD 的 LASIK 患者术前1周接受热脉动治疗(n=32)较未治疗对照组(n=26)在术后3个月时 OSDI 和 TBUT 改善更显著, 后续对对照组实施相同治疗也证实该效果[951].综合现有证据, 对拟行白内障和屈光手术的干眼病患者(尤其是蒸发过强型)实施积极干预可改善术前腺体功能,优化手术体验[939,950]并提升术后视觉质量[952], 支持将其作为未来的标准诊疗方案.

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手术治疗

• 永久性泪点封闭：永久性泪点封闭可通过多种技术实现，其中最常见的是泪点电灼术.其原理与泪点栓或泪小管栓类似，通过增加结膜囊泪液储留发挥作用[953](详见6.2.3节).泪点电灼术通常适用于临时栓子治疗有效但无法长期保留或耐受栓子的患者[954].一项纳入80例患者的回顾性研究显示，电灼术后中重度干眼病比例显著降低，总再通率为21%，且规律使用局部激素者再通率更高[954,955].慢性瘢痕性疾病患者的再电灼可能最低(可能与基础疾病相关的纤维化有关)，65例此类患者电灼术后再通率仅11%，且患者对再次电灼的反应良好[956].该研究中电灼术的主要适应证为移植物抗宿主病(36例)和原发性干燥性角结膜炎(15例)，54%患者报告症状显著改善,角膜染色减轻[954]，且临床操作简便,并发症少.

另一项研究报道，23例中重度干眼病患者接受下泪点电灼术后3个月，TBUT，OSDI评分和角膜染色改善，角膜基底膜下神经密度增加[957].对7例(11眼)重度干眼病患者实施的泪小管消融联合泪点缝合术显示再通率低，术后1年干眼病主客观指标均显著改善[958].

一项系统综述分析了热灼或手术永久封闭泪点治疗干眼病的疗效[959].纳入的9项单臂研究中，5项采用热电灼，4项采用手术封闭.最终随访时两组 Schirmer I和TBUT改善相似，热电灼组再通率0-38.7%，手术组5-9%，其中一次性热电灼笔再通率低于单极射频电灼.研究者认为两种方法改善泪液量的效果相当且再通率相近[959]，但仍需高质量 RCT 进一步验证疗效.

• 睑裂缝合术：睑裂缝合术是通过缝合眼睑外侧部分以缩小睑裂高度的外科技术，其通过减少暴露眼表面积来保护角膜并改善眼表微环境.根据缝合方式是直接缝合于眼睑，还是通过切除或切开睑缘造成创面，睑缘缝合术可分为暂时性缝合和永久性缝合.该手术主要适用于神经营养性角膜病变,兔眼症以及 Stevens-Johnson 综合征等眼表疾病的治疗[960–962].对于局部治疗未能改善角膜上皮健康状况或出现反复上皮缺损的重度干眼病患者，也可考虑实施该手术.目前关于睑裂缝合术治疗干眼病疗效的文献证据较为有限.

• 眼睑异常的手术治疗：

肉毒素注射

肉毒梭菌产生的肉毒素，通过抑制神经肌肉接头的乙酰胆碱释放发挥作用[963].在眼科领域，该毒素广泛应用于多种适应症，包括作为眼睑痉挛和半侧面肌痉挛的一线治疗[964,965]，还可用于诱导保护性上睑下垂(治疗持续性上皮缺损或溃疡)[966,967],管理甲状腺眼病相关的睑裂退缩[968],矫正睑内翻[969,970]，以及治疗难治性丝状角膜炎[971].近年来，其作为干眼病治疗选择也获得关注[40,972–974].

研究表明，下睑内侧注射肉毒素可改善干眼病体征和症状，包括延长TBUT,提高 Schirmer 试验值,降低MMP-9 水平,减轻角膜荧光素钠染色及改善 OSDI 评分，这些益处在多项随机试验[975,976]和其他研究[838,977]中得到验证.此外，一项研究指出，与泪点栓和常规局部治疗相比，肉毒素能更显著改善LASIK术后干眼症状且并发症更少[972].

特发性眼睑痉挛是一种累及眼周及额肌的局灶性颅肌张力障碍.研究显示40-60%患者伴有干眼症状和 Schirmer 试验值降低[965,978–980]，且其泪液中促炎细胞因子水平显著高于单纯干眼病患者[981].肉毒素注射通过暂时性化学去神经支配作用，可改善这类患者的干眼症状并恢复泪膜稳态，表现为 TMH 增厚,TBUT 延长,泪液清除时间缩短及LLT增加[973,977,981–984]，但疗效仅维持3个月[985].需注意的是，注射部位过于接近泪腺可能抑制泪液分泌[974,980,986]，一项 RCT 报告约19%患者注射后出现眼干症状[987].

皮肤松弛症

皮肤松弛症表现为眼睑皮肤松弛冗余，多与衰老相关.研究显示，46-51%的皮肤松弛症患者存在干眼症状，而55-86%的患者报告上睑成形术后主观症状改善[988–990].然而，术后泪液渗透压，Schirmer 试验值,TBUT 及结膜染色评分等客观指标均未显著改善.此外，联合上睑下垂矫正术(Müller肌-结膜切除术)与单纯睑成形术相比，多数研究发现其未对上述结局产生影响[988,990,991]，仅有一项研究表明联合手术后干眼病体征和症状加重，而单纯眼睑成形术则无此现象[992].该类手术前后症状与体征改善的不一致性仍需进一步研究阐明.

睑内翻与睑外翻

睑内翻与睑外翻可导致眼表暴露，引发干眼症状，其中睑内翻常伴发倒睫[993].面神经麻痹可因岩浅大神经麻痹继发眼轮匝肌功能减退，导致麻痹性下睑外翻及上睑退缩[994].其他致病因素包括创伤(化学性/机械性/手术性),肿瘤,面部手术及年龄相关性睑松弛[995].

手术矫正是主要治疗手段，包括眦腱紧缩术,瘢痕或机械性因素切除等[996–997].研究证实，睑内翻矫正可改善视力,点状角膜病变及 TBUT,但 Schirmer 试验结果无变化[998].另有研究表明，睑缘缝合术可有效矫正睑内翻并促进重度干眼病患者上皮愈合[962].

一项比较研究评估了四种下眼睑内翻修复术式组合，一类用于治疗水平松弛，另一类用于治疗垂直松弛.水平松弛手术包括外侧睑板条状切除术和Bick术，而垂直松弛手术包括外翻缝合和下睑提肌折叠术.结果显示Bick术复发率及并发症低于外侧睑板条状切除术[999].对于中重度睑内翻，原发性与复发病例均可采用口腔黏膜移植[1000]，研究报道瘢痕性睑内翻行唇黏膜移植后83%患者症状完全缓解，复发率为11%[1001].

兔眼症

兔眼症指眼睑闭合不全或缺陷导致的角膜暴露.持续或严重病例需手术干预，可选方案包括:上睑配重植入,弹簧丝植入,眼睑重建及部分/完全性睑裂缝合术[468,1002,1003].上睑利用其自身的重力实现被动闭眼.黄金因其安全性和高密度被广泛使用，但最新研究表明铂

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金因修正率低,脱出风险小, 且密度更高,设计更薄从而改善美观度的优势, 具有更优预后[1004,1005].

当上睑手术后仍存在角膜暴露时, 可通过多种技术实现下睑抬高.研究显示, 采用耳廓软骨移植(同时应用于上下睑)可使80%轻中度兔眼患者实现有效眼睑闭合[1006].硬腭黏膜移植亦可抬高下睑以增强眼表保护[1007].外侧睑板条状切除术通过紧缩和复位下睑, 能改善睑球贴合度, 减少麻痹性睑外翻患者的角膜暴露和溢泪[1008].

- 眼表解剖结构异常的手术治疗:

结膜松弛症

对于润滑剂,局部环孢素或泪点封闭治疗无效的重度结膜松弛症, 可考虑手术切除多余结膜组织[1009].现有技术包括:电凝/热灼术[1010,1011],结膜结扎术[1012],巩膜固定术[1013],氩激光结膜成形术[1014],手术切除术[1015,1016]以及近年应用的高频射频消融术[834,1017,1018].各类技术均可实现75%以上患者的症状改善, 但热灼术和切除术可能因过度烧灼或缝合导致复视,睑球粘连及结膜下出血等并发症[830,1019].相比之下, 高频射频消融术可通过低能量操作减少热损伤,降低瘢痕风险且无需缝合, 在消除冗余结膜的同时促进愈合[830].

翼状胬肉与睑裂斑

翼状胬肉与睑裂斑是常见的眼表疾病, 均以结膜及角膜缘组织异常增生为特征, 其中翼状胬肉向角膜延伸可能导致视力损害[1020].其通过破坏泪膜稳定性,导致泪液分布不均及蒸发增加, 从而加重干眼症状并改变泪液渗透压[1021–1022].手术仍是目前最有效治疗方式, 研究显示其可通过恢复眼表解剖结构和泪膜功能带来长期获益[838,845].

目前已有多种手术技术被探索应用.近期的 Meta 分析表明, 角膜缘-结膜自体移植术通过减轻炎症和促进愈合, 能带来最佳长期眼表预后效果[1023,1024].但该技术存在获取角膜缘及结膜组织时可能导致角膜损伤的风险.羊膜移植术作为替代方案, 既可保留角膜缘又具有术后早期恢复优势[1023].与单纯胬肉切除术相比, 角膜缘-结膜自体移植和羊膜移植均显示出更低的复发率[1025].常用辅助治疗包括CsA,丝裂霉素C,5-氟尿嘧啶,β射线照射以及大分子和小分子抗血管内皮生长因子制剂, 各类药物均具有相对应的副作用[1026,1027].

- 唾液腺移植术: 唾液腺转位术通过补充唾液分泌改善眼表润滑, 为严重干眼病患者提供治疗选择[1028].泪腺与唾液腺具有相似的组织结构和自主神经支配[1029], 该手术适用于先天性或获得性无泪症,面神经麻痹, Stevens-Johnson 综合征或化学伤等慢性瘢痕性疾病导致的严重干眼病.移植腺体可来源于大唾液腺(腮腺,颌下腺)或小唾液腺, 术前需对供体腺体进行细致评估[1029].对于干燥综合征,移植物抗宿主病和放疗等同时累及泪腺与唾液腺的疾病, 应避免自体移植[1030–1031], 此时需通过 HLA 配型后进行同种异体移植[1029,1030].

大唾液腺移植

腮腺移植因可能引发味觉反射性分泌, 且由于其浆液性分泌物特性, 临床上较少应用[1029].颌下腺移植采用自体血管化颌下腺移植至颞窝, 腺管经皮下通路植入结膜穹窿[1029].多项研究报道该技术可使 Schirmer 试验值提升≥15mm, 并改善 TBUT ,角膜染色评分及最佳矫正视力[1029,1032,1033].但移植后泪液渗透压降低可能导致角膜水肿, 需移除移植物[1033,1034].约半数 Stevens-Johnson 综合征患者因移植腺体随时间发生萎缩变性, 泪液分泌改善无法持续[1035].该术式的其他并发症包括移植物坏死,感染,瘘管形成,导管梗阻/狭窄及涎石症[1029].

小唾液腺移植

该术式将小唾液腺移植至上下结膜穹窿, 操作更简便且无需口腔外科医师参与[1036,1037–1038].对于伴睑内翻的重度干眼病患者, 可联合唇黏膜移植将小唾液腺植入上睑板全层开口, 同步改善眼睑错位和眼表润滑[1039].临床试验显示其可改善眼表染色评分, TBUT 和视力, 减少对人工泪液的依赖[1040–1041], 但可能发生移植物坏死,感染,上睑下垂及供区肉芽肿等并发症[1029,1040].比较研究显示颌下腺移植对重度干眼病效果更优, 而小唾液腺移植对轻中度干眼病改善更显著[1042].

- 泪腺神经再支配术: 近期报道的新型手术技术旨在为面神经麻痹导致的神经源性干眼病患者重建泪腺神经支配.初步的小样本研究 (n=10) 显示, 术后1年患者满意度高, Schirmer 试验值改善且人工泪液依赖减少[1043].同一组患者(n=9)在 87±15个月(60-108个月)个月的随访后报告了良好的长期疗效, 主观满意度,泪液分泌试验,角膜移植术后TBUT 和角膜荧光素染色均有所改善[1044].

治疗决策路径

目前对眼表疾病发病机制的理解, 既认识到患者体征和症状的异质性, 也认识到这些体征和症状的多种致病驱动因素.简单将患者划分为干眼病“亚型”(如水液缺乏型干眼病或蒸发过强型干眼病), 无法解释体征和症状的多种驱动因素可能同时存在, 并且可能随着时间的推移和治疗依从性而变化.试图将患者划分为离散类别(如轻,中,重度;1,2,3或4期;水液缺乏型或蒸发过强型干眼病等)的分期或分级系统对干眼病而言并非是最佳架构, 并且可能导致决策过程中忽略有效的治疗干预措施, 因为现行的分类方法无法充分反映引发干眼病体征与症状的多种致病驱动因素所具有的复杂和动态的本质.

通过参考 TFOS DEWS III 《诊断方法报告》[1]中的信息, 可以确定干眼病患者最可能的临床相关驱动因素.通过查阅本《管理与治疗报告》中的信息, 临床医生可以评估支持多种可用治疗方案的证据, 并将这些方案与特定患者存在的临床相关症状和/或体征驱动因素相匹配.考虑到干眼病具有多种致病驱动因素, 联合使用多种治疗可能是最合适的管理策略.治疗与致病驱动因素的对应关系见 图 3,4 和5.

对于有高质量人体研究支持其应用的治疗方案, 本报告采用特定标记注明(ü表示与安慰剂对照, þ表示与其

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基于病因的检查方法
脂质
泪膜脂质层厚度/干涉成像法
睑板腺分泌
睑脂质量
水液
泪河高度
试纸泪河计/Schirmer*/酚红棉线
粘蛋白/糖蛋白
丽丝胺绿/虎红染色
结膜印迹细胞学

基于循证证据的治疗方法
脂质
泪液补充剂/稳定剂(脂质模拟物)
泪液保存设备(湿房镜)
促进泪液分泌/恢复的药物
设备驱动的泪液分泌/恢复
眨眼治疗
局部睑缘清洁
水液
口服营养素(Omega 3)
泪液补充剂/稳定剂
泪液保存设备
药物/设备驱动的泪液分泌/恢复
局部抗炎药物
眼表再生药物
手术治疗
粘蛋白/糖蛋白
泪液补充剂/稳定剂(羟丙基瓜尔胶)
局部抗炎药物
促进泪液分泌的药物
设备驱动的泪液分泌(神经调节)

分类	章节	示例	脂质	水液	粘蛋白/糖蛋白
生活方式建议	5	可控危险因素	所有类型干眼均需考虑		
口服营养素	12	Omega 3 维生素 天然物质		✓ Omega 3	
泪液补充剂/稳定剂	6.1	人工泪液 润滑剂	✓ 脂质模拟物	✓ 人工泪液	
泪液保存装置	6.2	泪点栓塞 湿房镜 接触镜	☑ 湿房镜	☑ 湿房镜 ？泪点塞、巩膜镜	
促进泪液分泌/恢复的药物	6.3	促分泌剂 神经调节	☑ 局部促泌剂	✓ 神经调节药物 ☑ 局部促分泌剂	#促分泌剂
设备驱动的泪液分泌/恢复	6.3	热敷和按摩设备 脉冲光治疗 低强度光疗法	✓内部和外部眼睑加热设备、IPL、LLLT ☑ IPL ？热敷	✓神经刺激 ✓☑ LLLT	✓ 神经刺激
眨眼治疗	7.1	眨眼练习	✓		
局部睑缘清洁(如：降低细菌载量)	7.2	擦拭巾/凝胶/泡沫剂 抗菌剂 微海绵睑缘去屑术	✓		
局部抗炎治疗	8	糖皮质激素 T细胞免疫调节剂	✓ 环孢素A	✓	✓
眼表再生	10.1	血清 血液制品		✓生物制剂	
手术	11，14	组织切除 泪小点栓塞 眼睑手术/睑裂缝合术		✓	

IPL=脉冲光治疗，LLLT=低强度光疗法。
注：治疗方案未按任何特定顺序列出，针对每位患者从所列出的选项中进行选择应与患者共同进行决策。详情请参阅相关文本。
空白单元格表示在某一治疗类别中尚未有足够证据支持。
药物治疗被认为具有直接的生物学作用（Fura 2006）。
*在可能的情况下，用非侵入性检查来代替侵入性检查。

#	仅有临床前证据
✓	RCT 有效性 vs 安慰剂
☑	RCT 有效性 vs 参考药物
?	存在争议

图 3. **根据 TFOS DEWS III 诊断标准(症状加泪膜不稳定,高渗和/或眼表染色的临床体征)对干眼病进行诊断后的亚分类指南.该图重点突出了与泪膜缺陷相关的干眼病亚型.上半部分提供了与病因列表(左),泪膜结构的示意图(中)以及与病因驱动因素对应的循证治理措施列表(右).下半部分为已确定的干眼病泪膜相关驱动因素和其循证医学证据的详细信息.干眼病亚型并非相互排斥,针对已确定的病因进行联合管理适合恢复泪膜和眼表稳态.**

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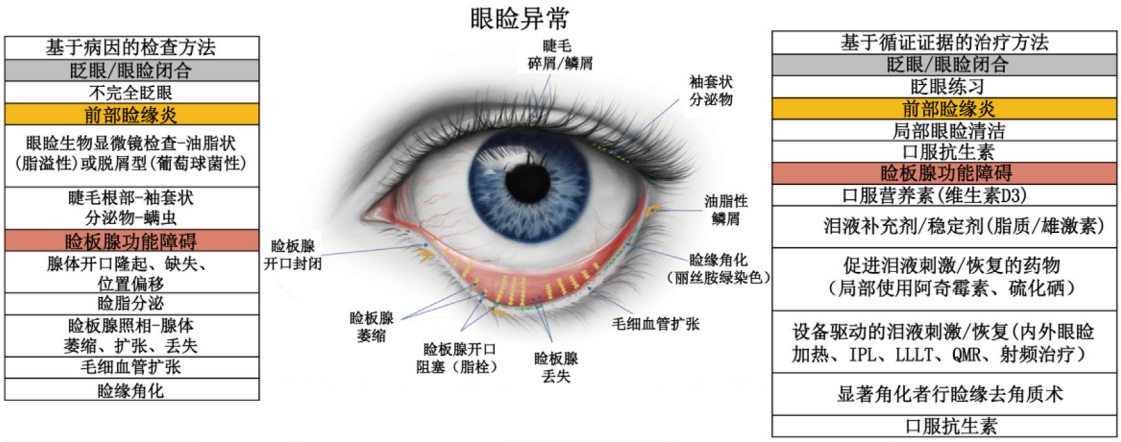

分类	章节	示例	眨眼/眼睑闭合	睑缘	
				前部睑缘炎	睑板腺功能障碍
生活方式建议	5	可控风险因素	所有干眼患者均需考虑		
口服营养素	12	Omega 3 维生素类 天然产物			✓ Omega 3 ？维生素D3
泪液补充剂/稳定剂	6.1	人工泪液 润滑剂			✓ 脂质模拟物
泪液保存装置	6.2	泪小点塞 湿房镜 接触镜	？湿房镜		
促进泪液分泌/恢复的药物	6.3	促分泌剂 神经调控			✓ 局部使用阿奇霉素、硫化硒
设备驱动的泪液分泌/恢复	6.3	热敷按摩设备 脉冲光治疗 低强度光疗法			✓内部及外部眼睑加热设备、IPL、LLLT、QMR
睑缘去角质术	6.3.1.3.2	角质术			☑ 当出现明显角化时
眨眼治疗	7.1	眨眼练习	✓		
局部睑缘清洁（如：降低细菌载量）	7.2	擦拭巾/凝胶/泡沫剂 局部抗菌剂 微海绵睑缘去屑术		✓	
局部抗炎治疗	8.2	糖皮质激素 T细胞免疫调节剂			✓ 环孢素A
口服抗生素	9	四环素类药物及其衍生物 大环内酯类		✓	✓
手术	11, 14	组织切除 泪小点栓塞 眼睑手术	✓		

IPL=脉冲光治疗、LLLT=低强度光疗法、QMR=量子分子共振电疗法。
注：治疗方案未按任何特定顺序列出，针对每位患者从所列出的选项中进行选择应与患者共同进行决策。详情请参阅相关文本。
空白单元格表示在某一治疗类别中尚未有足够证据支持。
当同一治疗类别中存在差异时，治疗方案需进行特异性命名。
药物治疗被认为具有直接的生物学作用（Fura 2006）。

✓	RCT 有效性 vs 安慰剂
☑	RCT 有效性 vs 参考药物
？	存在争议

图 4. **眼睑相关干眼病亚型及其对应治疗措施.**

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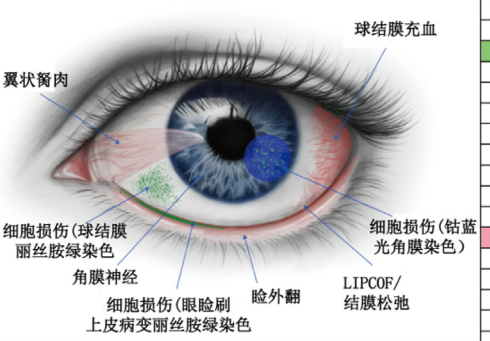
基于病因的检查方法
解剖异常
生物显微镜(如：翼状胬肉)、LIPCOF/结膜松弛、睑内翻/睑外翻、兔眼
神经功能障碍
角膜知觉
角膜活体共聚焦显微镜
细胞损伤/破坏
角膜(荧光素钠染色)
球结膜（丽丝胺绿染色）
眼睑刷上皮病变（丽丝胺绿染色）
炎症/氧化应激
球结膜充血
炎症标志物

眼表异常



基于循证证据的治疗方法
解剖异常
手术
神经功能障碍
泪液补充剂/稳定剂
手术(泪小点栓塞)
细胞损伤/破坏
口服营养素(维生素D3)
泪液补充剂/稳定剂
促进泪液分泌/恢复的药物
设备驱动的泪液分泌/恢复
局部睑缘清洁
局部抗炎治疗
眼表再生
手术(泪小点栓塞)
炎症/氧化应激
口服营养素(omega 3/维生素D3)
泪液补充剂/稳定剂
促进泪液分泌/恢复的药物
设备驱动的泪液分泌/恢复(IPL)
局部睑缘清洁/去角质术
局部抗炎治疗
眼表再生(羊膜)
手术(泪小点栓塞)

分类	章节	章节	解剖异常	神经功能障碍	细胞损伤/破坏	炎症/氧化应激	
						原发性	继发性
生活方式建议	5	可控危险因素	所有干眼患者均需考虑				
口服营养素	12	Omega 3、维生素 天然产物			✓ 维生素D3		✓ Omega 3、维生素D3
泪液补充剂/稳定剂	6.1	人工泪液 润滑剂		✓ 维生素A/B12/抗坏血酸	✓透明质酸、海藻糖、黄原胶、全氟己基辛烷和羟丙基瓜尔胶		✓ 透明质酸、神经物质P、黄原胶和羟丙基瓜尔胶、血清
促进泪液分泌/恢复的药物	6.3	促泌剂 神经调节			✓ 口服促泌剂 ☑ 局部促泌剂、神经调节药物		✓神经调节药物
设备驱动的泪液分泌/恢复	6.3	热敷和按摩设备 脉冲光治疗 低强度光治疗			✓ LLLT、QMR、神经刺激 ？IPL、探通术 ？外部眼睑加热、局部神经促分泌剂		☑ IPL
睑缘去角质术	6.3.1.3.2	去角质术					？
局部睑缘清洁(如降低细菌复合)	7.2	擦拭巾/凝胶/泡沫剂 抗菌剂、睑缘去屑术			？		？
局部抗炎治疗	8	糖皮质激素 T细胞免疫调节剂			✓	✓	
眼表再生	10	羊膜、胰岛素 生物制剂		？生物制剂	✓☑ 润滑素 ✓生物制剂	✓羊膜	
手术	11,14	组织切除、泪点栓塞、眼睑手术/睑裂缝合	✓	？泪点栓塞	？泪点栓塞		？泪点栓塞

IPL=脉冲光治疗、LLLT=低强度光疗法、QMR=量子分子共振电疗法。
注：治疗方案未按任何特定顺序列出，针对每位患者从所列出的选项中进行选择应与患者共同进行决策。详情请参阅相关文本。
空白单元格表示在某一治疗类别中尚未有足够证据支持。
当同一治疗类别中存在差异时，治疗方案需进行特异性命名。
药物治疗被认为具有直接的生物学作用（Fura 2006）。
原发性炎症被认为与潜在的全身性疾病有关，而继发性炎症则与干眼有关。

✓	RCT 有效性 vs 安慰剂
☑	RCT 有效性 vs 参考药物
？	存在争议

图5. 根据 TFOS DEWS III 诊断标准（症状加泪膜不稳定、高渗和/或眼表染色的临床体征）对干眼进行诊断后的亚分类指南。该图重点突出了与眼表相关的干眼亚型。图的上半部分提供了病因列表（左）、眼表疾病相关干眼示意图（中，由英国Optimed Ltd.公司提供）以及与其对应的循证治疗措施列表（右）。图的下半部分为已确定的眼表疾病导致干眼以及其循证医学证据的详细信息。干眼的亚型之间并非相互排斥，针对已确定的病因进行联合管理，有助于恢复泪膜和眼表稳态。

Fura, A. 2006. 'Role of pharmacologically active metabolites in drug discovery and development', *Drug Discov Today*, 11:133-42.

图 **5. 眼表相关干眼病亚型及其对应治疗措施.**

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他治疗比较)."。"表示本报告引用的研究中仅部分研究证实了该作用机制并观察到治疗的积极反应.为方便参考, 这三个表格将以附件形式呈现.

总结与结论

TFOS DEWS III《管理与治疗报告》提供了一个全面的,基于研究证据的框架, 用于优化干眼病的管理.该报告概述了基于个体疾病病因驱动因素的治疗方法.一线治疗包括改变眼部生活方式,补充泪膜和调整环境以稳定泪膜.睑板腺功能障碍是蒸发性干眼病的主要诱因, 可通过热敷,眼睑按摩,诊室加热设备,强脉冲光 (IPL),低强度激光治疗 (LLLT) 和新兴外用药物进行治疗.对于原发性炎症或免疫介导因素的患者, 应考虑使用皮质类固醇,环孢素 A (CsA) 和立他司特 (lifitegrast) 等抗炎疗法, 以及包括自体血清和 PRP 在内的生物泪液替代品.眼睑卫生习惯, 包括抗螨形螨治疗和眼睑剥脱术, 可进一步加强对眼睑疾病的管理.新型药理学和神经调节疗法已显示出促进泪液分泌的潜力.

对于难治性或重症患者, 更高级别的干预措施包括羊膜移植和各种手术方案.新兴方法不断拓展治疗的可能性.目前已开发出一种处方算法, 以帮助临床医生根据患者的病因选择合适的干预措施.

总而言之, 干眼病的管理需要个性化,多层面的策略, 并考虑患者潜在病因和个体因素.虽然泪液补充剂仍然是治疗的基石, 但越来越多的证据支持提高睑板腺功能和调整生活方式的重要性.随着新型治疗方法的出现, 未来的研究应侧重于改进现有治疗方案和寻找生物标志物以指导靶向治疗. TFOS DEWS III 旨在促进更好明确干眼病患者的病因驱动因素, 并将其与已证实的治疗作用机制和治疗方案相匹配, 从而改善患者的治疗效果和生活质量.

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CONFLICT OF INTEREST

None

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