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小切口基质透镜取出术后干眼症发病机制的研究进展

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摘　要

近视在全球发病率逐年增加，据估计，到2050年，全球近视人数将接近50亿。随着屈光手术的发展，小切口基质透镜取出术(Small Incision Lenticule Extraction, SMILE)由于其有效性和安全性，在临床上广泛应用，现已成为不少年轻人矫正屈光不正的首选。尽管它在医患群体中都非常受欢迎，但与其他角膜类屈光手术一样，干眼症是其术后最常见的并发症，也是患者术后满意度下降的主要原因。术后干眼症不仅影响患者的生活质量，还会导致威胁视力的其他并发症。近年来，研究发现SMILE术后干眼症由多因素共同作用，了解SMILE术后干眼症发病机制更有助于临床治疗。

关键词

屈光手术，小切口基质透镜取出术，干眼，角膜神经

Research Progress on the Mechanism of Dry Eyes after SMILE

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Abstract

The global incidence of myopia is increasing year by year, and it is estimated that by 2050, the number of myopic people worldwide will be close to 5 billion. With the development of refractive surgery, small incision lenticule extraction (SMILE) has become the first choice for many young people

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to correct refractive errors due to its effectiveness and safety. Although it is very popular among doctors and patients, dry eye syndrome, like other corneal refractive surgery, is the most common complication after surgery and the main reason for the decline in postoperative patient satisfaction. Postoperative dry eye not only affects the patient's quality of life, but can also lead to other sight-threatening complications. In recent years, it has been found that dry eye syndrome after SMILE is multifactorial, and understanding the mechanisms of dry eye syndrome after SMILE is more helpful for clinical treatment.

Keywords

Refractive Surgery, Small Incision Lenticule Extraction, Dry Eye, Corneal Nerve

1. 引言

角膜屈光手术后干眼症的发病机制并不单一，可能与角膜神经切断、术后炎症反应、结膜杯状细胞受损、泪膜不稳定以及术后用药带来的毒副作用有关，为多种因素共同作用的结果。小切口基质透镜取出术是近年来出现的一种新的角膜屈光手术，它通过飞秒激光在角膜层间制作一个基质透镜，并通过微小切口将透镜取出，以达到矫正近视的目的[1]。与其他角膜屈光手术相比，它不产生角膜瓣，对角膜的侵入性小，术后角膜生物力学更加稳定[2] [3]。但有研究[4]-[9]仍然观察到 SMILE 术后患者会产生干眼症，更甚者会在相当长的一段时间内持续存在干眼症。本文就 SMILE 术后干眼症可能的发病机制进行综述。

2. 角膜神经损伤

角膜神经的切断在屈光手术后干眼症的发生中有着不可忽视的作用。角膜神经以放射状的方式从外周向中心进入，在前弹力层下形成上皮下神经丛，穿透前弹力层形成基底下神经丛，最终产生角膜终末神经[10] [11]。SMILE 手术以飞秒激光进行两次扫描制作角膜基质透镜，在侧方做一小切口，用特殊的镊子将透镜从此切口取出，在这一过程中，角膜切口处的周围神经纤维依然会被切断。此外，在基质透镜区域内穿过前弹力层的神经纤维也会被切除，即使与其他角膜屈光手术方式相比，SMILE 术后角膜神经影响较小[12]。

2.1. SMILE 手术对角膜神经的影响

SMILE 手术对角膜神经形态、密度、分布和角膜敏感性均存在一定的影响[12]-[14]。2014 年，研究人员对兔子眼睛实施了 SMILE 手术，用免疫染色观察兔角膜切片以及提取的角膜基质透镜，发现术后治疗区域的中心、上、下、鼻和颞的角膜神经长度和密度均减少[15]。Yang [16]等人用共聚焦显微镜观察到 SMILE 术后 1 周的角膜基底下神经密度显著降低。有趣的是不同帽的厚度对角膜神经的破坏无显著差异，但是只比较了 100 μm 和 120 μm 的帽厚度，且观察时间点仅为术后 1 周。在另一项相似的研究中，Song [17]等人对 3 组角膜帽厚度(110 μm、120 μm、130 μm)进行了为期 6 个月的观察，110 μm 组角膜基质下神经定量值显著低于 120 μm 和 130 μm 组，尤其是在术后 1 周。有学者还发现，高度近视的患者 SMILE 术后对角膜神经的影响更大，且矫正的等效球镜度数与角膜神经纤维密度、角膜神经分支密度、角膜神经纤维长度、角膜神经纤维面积和神经纤维分布均呈显著负相关[18]。可以理解的是，在高度近视矫正中，基质

消融范围大，因而受到影响的角膜神经更多。与之相反的事实是，Denoyer [19]报告说，SMILE 手术组的角膜神经变化不显著。这可以解释为，整个基底下神经丛是一个相互连接的网络，有几个较大的神经干通过基质神经将冲动传递到角膜缘传入神经及更远的地方。SMILE 手术虽然切断了一些基质神经，但某些仍然存在的神经可以传递来自整个基底下神经丛的信息，从而保持功能完整性，这也解释了为何有的研究表明 SMILE 术后干眼指标并无恶化[20]，但角膜神经纤维数量与干眼指标的相关性还需要进一步研究。

2.2. 角膜神经切断引发干眼症的机制

2.2.1. 损伤眼表－泪腺神经通路

角膜神经具有感觉功能，感觉输入参与保护性的眨眼反射，同时也是驱动泪腺分泌泪液的传入成分[21]。角膜神经被切断会破坏眼表－泪腺神经环，通过影响角膜敏感性、泪腺分泌、眨眼反射导致干眼[11] [21]。SMILE 手术除了激光消融基质内神经外，在取出透镜的切口处也切断了部分神经，角膜部分失去神经支配从而降低了角膜敏感性。Lee 等人[22]在其构建的小鼠模型中发现，单侧角膜神经切断能够减少泪腺泪液的分泌，有趣的是，这种减少发生在小鼠的双侧泪腺，这种现象可能与神经通路的逆向传导有关。目前最新的一项研究进一步揭示了微观层面的发生机制，这种单侧角膜神经切断通过 VIP/Hif1a/TfR1 通路诱导双侧泪腺细胞铁死亡从而导致泪腺分泌减少，为角膜屈光手术诱导的干眼症带来了有前途的新治疗靶点[23]。同时，角膜去神经支配导致眨眼反射减少，眨眼率下降，泪液蒸发过强，泪膜不稳定从而引发干眼[24]。

2.2.2. 诱发眼表炎症反应

与伤口愈合相关的炎症反应在 SMILE 术后干眼的发病中也有所参与[25]。这是一种神经源性的炎症反应，即由神经介质介导的炎症。角膜神经可以释放各种神经递质以及神经肽、神经营养因子，包括 P 物质(SP)、降钙素基因相关肽(CGRP)、血管活性肠肽(VIP)等[26]。SMILE 手术切断部分角膜神经，诱发角膜伤口的愈合，启动一系列免疫级联反应。在此过程中，泪液神经介质的释放会改变泪液成分，破坏泪膜稳态，引发干眼症，导致患者的不适[25] [27]。一项观察性研究中，研究人员发现在用环钻切断小鼠角膜神经后的 2 周，双侧角膜和结膜中的免疫细胞增加。基于此，他们假设单侧角膜神经损伤可能会破坏双侧眼表免疫稳态并导致干眼症的发生发展[22]。Gao 等人[28]报道了 SMILE 术后早期患者泪液中白介素-6 (IL-6)和神经生长因子(NGF)升高，不同的是 IL-6 在术后 1 个月即恢复到术前水平，而 NGF 在术后 3 月才恢复。NGF 是一种主要由角膜上皮和基质表达的神经营养物质，在角膜伤口愈合过程中触发其释放。Liu [29]曾提出假设，尽管飞秒激光精确地只消融角膜基质制作屈光透镜，但在此过程中可能会逸出少部分能量，造成轻微的上皮损伤并触发炎症反应。SMILE 手术涉及两次飞秒激光扫描，因此 SMILE 手术上皮受影响更大，可以解释 NGF 在术后 3 月才恢复到基线水平。尽管如此，这只是一种假设，未来需要更多研究证据来支持。值得注意的是，研究表明，在高度近视的 SMILE 术后人群中，表现出 SP 和 CGRP 的显著升高[27]。这一点与 SMILE 术后观察到的高度近视对角膜神经影响更大相符。

2.2.3. 去神经支配导致上皮屏障功能受损

上皮屏障功能受损可以看作是干眼症的严重表现。角膜神经除了感觉功能以外，还具有营养功能，它能释放大量神经介质从而保证上皮细胞的健康[21]。这些神经介质对上皮－神经相互作用至关重要。神经和细胞之间存在相互支持和依赖的循环，上皮细胞和角膜神经相辅相成，不仅角膜神经能够分泌神经营养因子营养上皮，上皮细胞反过来也会分泌细胞因子维持神经的健康和再生。角膜感觉传入神经切断导致上皮营养障碍，上皮细胞对神经的营养作用丢失，在此过程中亦可诱发眼表炎症反应，导致角膜上皮的屏障功能受损，由此所致的恶性循环，其最终结果为眼表环境的失衡，从而产生干眼症。

2.3. SMILE 术后角膜神经变化与干眼症的关系

角膜神经、神经介质和干眼症之间的相互关系需要进一步阐述。一项最新的屈光术后观察研究发现，单侧 SMILE 术后患者表现出双侧角膜的改变，其中包括神经退行性改变、角膜敏感性降低、干眼症状恶化和泪液神经介质的变化。在 SMILE 组中，角膜敏感性与角膜神经纤维长度呈正相关，与干眼症严重程度呈负相关，SP 和 NGF 在泪液中的水平与角膜敏感性呈负相关，但与干眼症严重程度呈正相关[30]。Liu 等人的实验证实，SMILE 术后随着角膜神经纤维面积以及角膜神经纤维分布的显著减少，泪液分泌量(Schirmer 试验值)也显著减少[18]。既往也有研究证实过，SMILE 术后 IL-6 水平与眼表疾病指数量表分数(OSDI)呈正相关，NGF 水平与角膜敏感性呈负相关[28]。另一项研究发现，NGF 水平与 OSDI 高度正相关，与泪膜破裂时间(BUT)负相关，转化生长因子-β1 (TGF-β1)与 BUT 负相关[31]。在人类中，泪液中的 CGRP 与角膜神经密度和敏感性之间的关系已得到证实[32]，然而，并未观察到 SP、CGRP、肿瘤坏死因子-α (TNF-α)、细胞间粘附因子-1 (ICAM-1)等其他神经介质在 SMILE 术后的变化以及其与角膜神经之间的关系，猜测可能与 SMILE 手术对角膜神经的影响不足以引起足够量的这些炎症介质释放有关，矫正屈光度越大，角膜神经及神经介质变化越显著可以用来解释这一点，但这其中的具体机制需要研究进一步阐明[27] [31]。SMILE 术后的角膜神经参数、泪液神经介质与干眼症的临床体征显著相关，这也间接揭示了 SMILE 术后干眼的潜在机制。

3. 损伤结膜杯状细胞

结膜杯状细胞分泌黏蛋白，是参与构成泪膜的重要组成成分[33]。在飞秒激光抽吸过程中，吸引环产生的负压很容易损伤角膜缘周围的结膜杯状细胞，其分泌的黏蛋白减少，导致泪膜不稳定，引发干眼症。一项关于激光原位角膜磨镶术(LASIK)的前瞻性研究观察到 LASIK 术后结膜杯状细胞密度的减少[34]，另一项研究证实了是 LASIK 手术中负压吸引对结膜杯状细胞的损伤导致了密度的减少[35]。有报道称，与使用微型角膜刀相比，使用飞秒激光对结膜杯状细胞的减少影响更大，并且结膜杯状细胞的减少与抽吸时间存在高度相关性[36]。SMILE 手术中同样使用飞秒激光，然而，目前并未报道关于 SMILE 手术对结膜杯状细胞影响，还需要更多的证据支持。

4. 泪膜分布异常及不稳定

飞秒激光消融后导致角膜形状的改变将影响眼表和眼睑之间的关系，导致泪膜分布异常，蒸发增加[37]。研究发现 SMILE 手术与飞秒激光辅助原位角膜磨镶术(FS-Lasik 手术)相比，导致角膜前表面更不规则，推测是因为其取出一中间厚、两边薄的角膜基质透镜，导致角膜更趋于扁平[38]。Zhang 等人[6]的研究表明 SMILE 后角膜表面不规则性会影响泪膜稳定性，BUT 值降低，并且，泪膜稳定性下降会改变角膜曲率，造成恶性循环。既往有学者发现屈光手术后会导致功能性睑板腺的减少，从而引发慢性泪膜功能障碍[37]。脂质层位于泪膜的最外层，由睑板腺细胞分泌，泪膜脂质层厚度(LLT)是评价泪膜稳定性的重要指标[39]。不完全眨眼会导致脂质分布不均以及增加蒸发，引发眼表不稳定的恶性循环，这会进一步加剧干眼症[40]-[43]。Li 等人[44]的研究发现 SMILE 术后 1 周、1 月的 LLT 显著下降，而不完全眨眼率上升，这些变化均表明泪膜稳定性下降，可能参与了 SMILE 术后干眼的发生。

5. 药物对角膜及结膜的毒性作用

局部药物的毒副作用会对角膜和结膜造成一定程度的损害[45]。SMILE 术前、术中、术后都会局部应用一些含有防腐剂的药物，例如抗生素滴眼液、表面麻醉剂、激素滴眼液等。苯扎氯胺是局部眼用制剂中应用最广的防腐剂，在多种动物模型以及人体外试验中已证实，苯扎氯胺对眼表的毒性作用[46] [47]。

有学者成功建立了苯扎氯铵局部给药诱导的小鼠干眼模型，并深入探讨了苯扎氯胺可能通过诱发眼表炎症反应从而导致干眼的机制[48] [49]。除了药物中防腐剂的毒副作用外，某些药物本身也会造成干眼症反应，这可能是由于长期应用局部药物导致的上皮屏障功能受损[50]。SMILE 术后会使用 0.2%酒石酸溴莫尼定或噻吗洛尔等局部制剂降眼压以及改善夜视环境下眩光等不适，它们作为 α 受体激动剂以及 β 受体阻滞剂已被证实会引起干眼[51] [52]。药物使用与 SMILE 术后干眼之间的关系还需大量临床研究证实。

6. 总结

干眼被定义为“一种多因素的眼表疾病，其特征是泪膜稳态破坏，并伴有眼部症状，其中泪膜不稳定和高渗性、眼表炎症和损伤以及神经感觉异常起着病因作用”[53]。归根到底，SMILE 术后干眼症的发生并不是由单一因素引起的，就以上探讨的可能机制之间，也有许多相互作用，例如角膜去神经支配、角膜伤口愈合可启动一系列免疫级联反应，诱发眼表炎症，眼表炎症又可破坏泪膜稳态，局部药物的毒副作用损伤眼表，诱导炎症，从而导致泪膜不稳定，表现为干眼，眼部干燥反过来将延迟角膜伤口愈合，导致更严重的后果。今后的研究方向可以从泪液基因组学、蛋白质组学、代谢组学深入，确认具体的分子靶点以及标志物，从而优化 SMILE 术后干眼的治疗。了解 SMILE 术后干眼的发生机制有助于确定新的治疗靶点，因此，临床上对待屈光术后干眼的管理策略得以进一步更新。

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