DOI: https://doi.org/10.17816/OV64116

评估应用前列腺素类似物的原发性开角型青光眼患者的视网膜厚度和白内障术后囊性黄斑水肿发生率

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目标: 评估前列腺素类似物和非甾体抗炎药对原发性开角型青光眼患者在进行超声乳化术并植入人工晶状体后的视网膜中央凹厚度和白内障术后囊性黄斑水肿发展的影响。

材料和方法: 共有91名患者被纳入研究。第一和第二观察组包括各22名应用前列腺素类似物的患者（22只眼睛）。对照组包括47名患者(57只眼睛)，不伴有青光眼。各组受试者术后都接受了皮质类固醇和抗生素，而第二组和对照组的患者还接受了非甾体类抗炎药。通过光学相干断层扫描来评估术前、术后2周、2个月和6个月视网膜中央区的厚度。

结果: 观察组中超声乳化术后视网膜中央凹的厚度增加，第一组在6个月后恢复到基线值，第二组在2个月后恢复到基线值，对照组在术后2周低于术前值，然后逐渐增加，但没有达到基线值。

结论: 在我们对应用前列腺素类似物患者进行超声乳化术和人工晶状体植入术后没有发现白内障术后囊性黄斑水肿。术后使用非甾体类抗炎药可以稳定视网膜的厚度，有助于恢复其正常厚度。

关键词: 视网膜厚度；中央凹；超声乳化术；原发性开角型青光眼；前列腺素类似物；白内障术后囊性黄斑水肿；非甾体类抗炎药；光学相干断层扫描。

引用本文：
Wang X, Astakhov SYu, Potemkin VV, Potemkina AR, Anikina LK. 评估应用前列腺素类似物的原发性开角型青光眼患者的视网膜厚度和白内障术后囊性黄斑水肿发生率. *Ophthalmology Journal*. 2021;14(2):17-26. DOI: https://doi.org/10.17816/OV64116

收稿日期: 2021年3月25日 **审稿日期:** 2021年4月25日 **出版时间:** 2021年6月25日

DOI: https://doi.org/10.17816/OV64116

Evaluation of retinal thickness and of pseudophakic cystoid macular edema incidence in patients with primary open-angle glaucoma treated with prostaglandin analogues

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BACKGROUND: Cataract is often associated with primary glaucoma. Prostaglandin analogues use is considered to be a risk factor for pseudophakic cystoid macular edema.

PURPOSE: To evaluate the effect of prostaglandin analogues and non-steroidal anti-inflammatory medications on the central retinal thickness and the incidence of pseudophakic cystoid macular edema after phacoemulsification with intraocular lens implantation in patients with primary open-angle glaucoma.

MATERIALS AND METHODS: 91 patients were enrolled in the study. The first and the second main groups included 22 patients (22 eyes) each. All patients in main groups had glaucoma and were treated with prostaglandin analogues. 47 patients (57 eyes) without glaucoma were included in the control group. After phacoemulsification, patients from all groups were treated with topical antibiotics and steroids. Patients in the main second and in the control groups received also non-steroidal anti-inflammatory drops. The retinal thickness was measured by optical coherence tomography 2 weeks, 2 months and 6 months after surgery.

RESULTS: After surgery, the foveal thickness in patients of the first and the second groups increased, but returned to the preoperative level after 6 and 2 months, respectively. The foveal thickness in the control group decreased after surgery, and it increased gradually but did not achieve the preoperative values.

CONCLUSION: Prostaglandin analogues use after phacoemulsification with intraocular lens implantation does not affect the incidence of pseudophakic cystoid macular edema. Prescribing non-steroidal anti-inflammatory drops after the surgery helps achieving more rapid normalization of the central retinal thickness.

Keywords: retinal thickness; fovea; phacoemulsification; primary open-angle glaucoma; prostaglandin analogues; pseudophakic cystoid macular edema; non-steroidal anti-inflammatory drops; optical coherence tomography.

To cite this article:
Wang X, Astakhov SYu, Potemkin VV, Potemkina AR, Anikina LK. Evaluation of retinal thickness and of pseudophakic cystoid macular edema incidence in patients with primary open-angle glaucoma treated with prostaglandin analogues. *Ophthalmology Journal*. 2021;14(2):17-26. DOI: https://doi.org/10.17816/OV64116

Received: 25.03.2021 **Accepted:** 25.04.2021 **Published:** 25.06.2021

DOI: https://doi.org/10.17816/OV64116

Оценка толщины сетчатки и частоты развития псевдофакичного кистозного макулярного отёка у больных первичной открытоугольной глаукомой, получающих аналоги простагландинов

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Цель. Оценить влияние аналогов простагландинов и нестероидных противовоспалительных препаратов на толщину фовеолярной сетчатки и развитие псевдофакичного кистозного макулярного отёка после факоэмульсификации с имплантацией интраокулярной линзы у больных первичной открытоугольной глаукомой.

Материалы и методы. В исследование включен 91 пациент. В первую и вторую основные группы вошли по 22 человека (22 глаза), получающие аналоги простагландинов. Контрольную группу составили 47 пациентов (57 глаз) без сопутствующей глаукомы. Исследуемые всех групп получали после операции кортикостероиды и антибиотики, пациенты второй основной и контрольной групп также получали нестероидные противовоспалительные препараты. Методом оптической когерентной томографии оценивали толщину центральной зоны сетчатки до и через 2 нед., 2 и 6 мес. после операции.

Результаты. Толщина сетчатки в фовеа после факоэмульсификации в основных группах была увеличена и вернулась к исходным значениям через 6 мес. в первой группе и через 2 мес. во второй, в контрольной группе — через 2 нед. после операции была ниже дооперационных значений, затем постепенно возрастала, но не достигла исходного уровня.

Заключение. У прооперированных нами пациентов, получающих аналоги простагландинов, после факоэмульсификации с имплантацией интраокулярной линзы псевдофакичный кистозный макулярный отёк не выявлен. Применение нестероидных противовоспалительных препаратов в послеоперационном периоде стабилизирует толщину сетчатки и способствует восстановлению её нормальной толщины.

Ключевые слова: толщина сетчатки; фовеа; факоэмульсификация; первичная открытоугольная глаукома; аналоги простагландинов; псевдофакичный кистозный макулярный отёк; нестероидные противовоспалительные средства; оптическая когерентная томография.

Как цитировать:
Ван С., Астахов С.Ю., Потемкин В.В., Потемкина А.Р., Аникина Л.К. Оценка толщины сетчатки и частоты развития псевдофакичного кистозного макулярного отёка у больных первичной открытоугольной глаукомой, получающих аналоги простагландинов // Офтальмологические ведомости. 2021. Т. 14. № 2. С. 17–26. DOI: https://doi.org/10.17816/OV64116

Рукопись получена: 25.03.2021 **Рукопись одобрена:** 25.04.2021 **Опубликована:** 25.06.2021

引言

众所周知，手术仍然是目前治疗白内障唯一有效的方法。白内障术后囊性黄斑水肿（PCME）是一个重要并发症，也是术后无痛性视力障碍的常见原因。

CME被定义为外丛状层和内核层的液体积聚，并伴有视网膜Müller细胞水肿。CME包括视网膜黄斑区细胞外空间（有时细胞内空间）的局部扩张[1]。根据发生的原因和机制，可以区分为糖尿病性CME（DME）、视网膜静脉阻塞性CME、PCME以及伴随炎症性疾病（葡萄膜炎）的CME。在我们的研究中只观察了PCME。

尽管PCME在40年前就有描述，但其发病机制仍然不清楚[2-6]。然而，发生PCME的风险因素是众所周知的。PCME是由血-视网膜屏障的破坏和/或复杂手术中玻璃体牵拉造成的[7，8]。在手术创伤期间，虹膜可以释放炎症介质（主要是前列腺素），破坏血流-视网膜屏障，增加术后炎症期间的血管通透性[9-11]。

发生PCME的风险因素包括：

1) 手术操作类型或手术切口类型[8,12]:
- 囊内摘除术—7-24%[7]，
- 囊外摘除术—2-6.7%[13]，
- 超声乳化术—以前0.1-2%[14]；

2) 术中因素:
- 手术显微镜的辐射强度[15]，
- 超声波的功率、持续时间和/或晶状体乳化器的不同类型和型号[16]；

3) 术中并发症[6]：后囊破裂、玻璃体脱出、晶状体皮质残留和玻璃体牵引[10，11，17]；

4) 眼前节炎症的严重程度。

通常，CME在术后4-12周发生[10,11,17]。

14-77%的白内障患者合并青光眼，超过50%的原发性开角型青光眼（POAG）患者使用药物降压[18]。前列腺素类似物（PGAs）不仅被广泛用作单一疗法，而且还被用于联合疗法。文献中有证据表明，使用PGAs和CME之间存在相关性。早期研究表明，PCME与POAG患者局部使用拉坦前列腺有关[19-21]。一些作者认为，PGAs可能是增加CME发生可能性的一个风险因素[22-24]。还有一种观点认为，CME的主要原因在于防腐剂，而不是PGAs的活性成分[19]。一些研究者认为，应用PGAs降眼压的POAG患者在超声乳化术后视网膜增厚可能是由于PGA破坏了假晶状体眼的血-水屏障[25-27]。尽管就这一问题发表了大量的论文，但在POAG患者超声乳化术加人工晶状体（IOL）植入术前和术后期间使用PGAs的安全性问题尚未得到解决。由于超声乳化术技术的改进，手术创伤和术后炎症反应已经明显减少，术中并发症也降到了最低。另一方面，在临床实践中，抑制前列腺素合成的非甾体抗炎药（NSAIDs）被广泛应用于术后预防CME[19]。

光学相干断层扫描是一种非接触、非侵入性的检查，可提供高分辨率的生物显微成像。随着光学相干断层扫描（OCT）的发展，荧光素眼底血管造影（FAG）已不再是CME的主要诊断方法[28，29]。

*研究目的：*根据OCT数据评估PGAs和NSAIDs对POAG患者超声乳化术加IOL植入术后视网膜中央凹厚度的影响以及术后PCME的发生率。

材料和方法

该研究包括从2018年3月到2020年10月在圣彼得堡国家公共卫生机构«第二市中心综合医院»接受手术治疗白内障的91名患者（101只眼睛）。观察期为6个月。其中，44名患者（44只眼睛）在伴随POAG的情况下患有白内障，并应用PGA单药降压治疗。这些患者被分为2个观察组。第一组包括22名患者（22只眼睛），年龄在61至87岁（平均年龄为74.4±7.4岁），术后按医嘱应用常规眼药水（抗生素和糖皮质激素）；第二组包括22名患者（22只眼睛），年龄在54至88岁（平均年龄为73.4±9.3岁），术后按医嘱应用抗生素、糖皮质激素和NSAIDs。对照组包括47名53至84岁的白内障患者（57只眼睛）（平均年龄为70.8±8.3岁），没有POAG，术后按医嘱应用抗生素、糖皮质激素和非甾体抗炎药物治疗。

患者纳入标准：
- PGAs代偿性单药治疗的POAG I-III期患者，
- 不同时期的单纯性白内障患者，
- 无术中并发症（后囊破裂、玻璃体脱出、晶状体皮质残留、虹膜外伤等）。

排除标准：
- 伴随系统性疾病，如糖尿病和类风湿性疾病，
- 伴随眼部病变（葡萄膜炎、«湿性»老年性黄斑病变、黄斑裂孔、继发性青光眼、视网膜血管疾病、玻璃体黄斑牵引综合征和屈光性弱视），
- 有手术和眼外伤史。

根据主诉、病史和客观仪器检查结果分析诊断白内障和POAG。所有患者在超声乳化术前后都进行了常规眼科检查包括：自动验光仪、视力检测、前房角镜检查、眼压测量、视野测量、裂隙灯和眼底镜检查；附加检查包括：RTVue 100（Optovue，美国）进行OCT检查。

观察组患者连续应用一种PGAs或前列腺素药物（拉坦前列腺、曲前列腺、他氟前列腺和比马前列腺）。使用ICare TA01i眼压计（芬兰）测量眼内压。通过静态（阈值）电脑视野计评估青光眼稳定的动态。使用RTVue 100光学相干断层扫描仪（Optovue，美国）基于视网膜厚度图协议进行了视网膜厚度研究和数据分析（视网膜厚度在1毫米区域）。该研究在术前、术后2周、2个月和6个月进行。

所有患者均由一位经验丰富的外科医生在Infiniti超声乳化仪（Alcon，美国）上进行了常规超声乳化术并植入不同型号的IOL。手术结束时记录了超声乳化术的超声波、时间和水力学参数。所有手术没有出现术中并发症。

在术后阶段，所有受试者都按照以下方案接受治疗。第一观察组的患者长期每晚滴注一次PGA，术后给予0.5%的左氧氟沙星，每天4次，持续2周，以及0.1%的地塞米松，持续4周，时间从每天4次到1次递减。在第二组中，额外给予了0.1%的奈帕芬胺，每天3次，持续4周。对照组采用了类似的术后治疗方案。

使用IBM SPSS Statistics Subscription进行统计学处理，计算均值和标准差，通过单因素方差分析（ANOVA）确定组间术前和术后OCT数据的差异。各组术前和术后测量结果的差异通过学生t检验来确定。皮尔逊相关系数分析被用来评估超声乳化术参数和视网膜厚度之间的相关性。

结果

所有患者在术前、术后2周、2个月和6个月时都进行了检查。

术后一天，所有患者通过裂隙灯观察发现都有中度球结膜混合充血，角膜清晰或有轻度角膜病变，眼前房有轻度闪辉（«+»/«++»），瞳孔对光反应保留，IOL处于正确位置。后囊完整且透明。所有患者术后都获得了较高的视觉功能（见表1）。整个观察过程中，眼压趋于正常（见表2）。

所有患者在术前和术后都在RTVue 100（Optovue，美国）上进行了OCT检查，视网膜厚度测量结果见表3。图1和图2显示了不同时间段视网膜中央凹厚度的变化。

在我们的研究中，Kolmogorov-Smirnov检验和方差分析显示，数值数据符合正态分布和均匀分布。对所有获得的结果进行了多重比较（LSD和Bonferroni检验）。

表格 1. 比较各组的视力，*M*±*SD*（*n*=101）

Table 1. Visual acuity in groups, *M* ± *SD* (*n* = 101)

组别	术前	术后		
		2周	2个月	6个月
I(*n*=22)	0.1±0.1	0.8±0.2	0.8±0.2	0.9±0.1
II(*n*=22)	0.3±0.1	0.8±0.2	0.9±0.2	0.9±0.1
对照组(*n*=57)	0.3±0.2	0.9±0.1	0.9±0.1	0.9±0.1

表格 2. 比较各组ICare眼压参数，*M*±*SD*（*n*=101）

Table 2. IOP by ICare in groups. *M* ± *SD* (*n* = 101)

组别	术前，mmHg	术后，mmHg		
		2周	2个月	6个月
I(*n*=22)	15.0±2.5	15.7±3.7	13.0±2.1	13.7±3.8
II(*n*=22)	15.4±1.9	16.9±4.8	15.0±2.4	12.8±3.4
对照组(*n*=57)	15.3±3.8	14.5±3.5	13.0±3.2	13.1±34

DOI: https://doi.org/10.17816/OV64116

表格 3. 比较各组视网膜中央凹厚度，*M*±*SD*（*n*=101）

Table 3. Foveal thickness in groups. *M* ± *SD* (*n* = 101)

组别	术前，微米	术后，微米		
		2周	2个月	6个月
I(*n*=22)	250.2±18.0	253.1±25.8	258.0±22.7	258.7±13.6
II(*n*=22)	248.1±22.5	251.0±21.9	250.2±17.3	241.3±14.6
对照组(*n*=57)	266.0±1.4	251.0±1.4	255.0±7.1	258.3±16.6

表格 4. 比较各组的超声乳化参数，*M*±*SD*（*n*=101）

Table 4. Parameters of phacoemulsification in groups, *M* ± *SD* (*n* = 101)

组别	累计消耗的能量，千焦	平衡盐液灌注，毫升	手术时间，分
I(*n*=22)	15.1±7.3	63.2±15.1	7.5±1.6
II(*n*=22)	8.1±4.3	55.3±15.0	6.8±1.9
对照组(*n*=57)	9.9±7.7	51.8±12.4	7.1±2.3

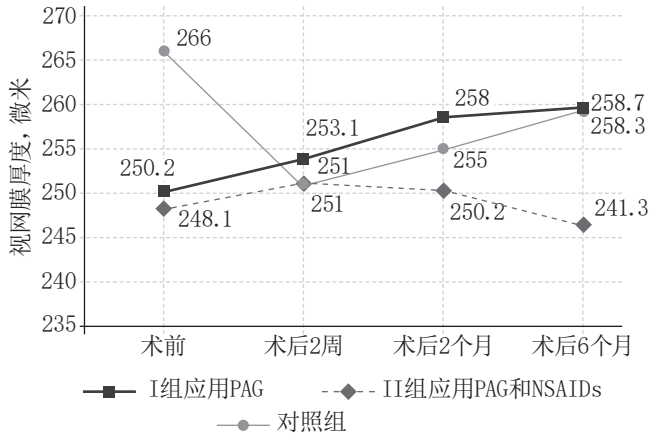

图.1. 比较各组在不同观察期视网膜中央凹厚度的动态变化

Fig. 1. Dynamics of foveal thickness at different follow-up periods in groups

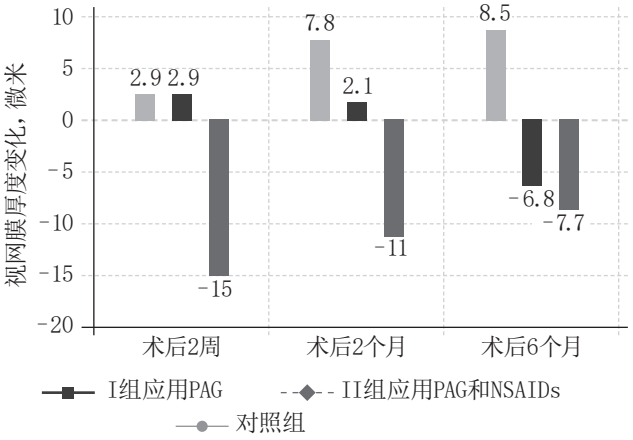

图.2. 比较各组不同观察期视网膜中央厚度与基线差异的动态变化

Fig. 2. Dynamics of the difference from the initial level of foveal thickness at different follow-up periods of observation in groups

术前、术后2周和2个月各组之间的视网膜厚度评估显示没有统计学差异（$p>0.05$），术后6个月第二组和对照组之间有统计学差异（$p<0.05$）。

各组之间术前和术后不同时间段视网膜厚度结果统计学上存在显著性差异（$p<0.001$）。

各组之间手术时间没有显著差异；但是，在累积消耗的超声能量和吸入的平衡盐溶液方面存在差异（$p<0.05$）（见表4）。然而，这些术中因素（累计消耗的超声能量、平衡盐溶液和手术时间）与视网膜中央凹厚度变化没有关联。

讨论

参与该研究的所有患者均未患有增加CME可能性的系统性或眼部疾病。此外，没有患者出现术中或术后并发症。该研究中没有患者被诊断出PCME。许多作者已经证明，在超声乳化术后使用PGAs不会增加CME发生的可能性[18,30,31]。

我们的研究结果表明，根据视网膜中央区一毫米的OCT数据，第一组患者手术后其厚度参数逐渐增加：2周后增加2.9μm，基线值的0.01%；2个月后增加7.8μm，基线值的0.03%；6个月后增加8.5μm，基线值的0.03%（见表4、5，图1、2）。我们的研究数据证实了Astakhov等人的结论[18]，即在超声乳化术后应用降压治疗6个月的患者，视网膜厚度增加，并在术后一年恢复到基线值。在2008年的一项研究中，术后没有使用NSAIDs，8周后所有研究组中超声乳化术后的视网膜厚度都有所增加，但在使用降压药物的POAG患者中，视网膜增厚是非POAG患者的两倍[27]。

表格 5. 在不同观察期，视网膜中央凹厚度的平均变化，*M*±*SD*（*n*=101）

Table 5. Mean change of foveal thickness at different follow-up periods, *M* ± *SD* (*n* = 101)

组别	术前，微米	术后，微米		
		2周	2个月	6个月
I(*n*=22)	250.2±18.0	2.9±7.8	7.8±4.7	8.5±4.4
II(*n*=22)	248.1±22.5	2.9±0.6	2.1±5.2	-6.8±7.9
对照组(*n*=57)	266.0±1.4	-15±0	-11±5.7	-7.7±15.2

在第一组和第二组中，术后2周视网膜中央厚度略有增加（+2.9μm，为基线值的0.01%）。然而，在第二组中，初始视网膜厚度恢复开始得更早（2个月后），所需时间更短（少于6个月，见表4、5，图1、2）。

有许多关于单纯性白内障超声乳化术后视网膜厚度变化的研究，术后给予抗生素和类固醇治疗。术后6个月中央视网膜厚度的增加不同（从17.33到23.68微米），保持在正常范围内[32,33]。然而，Ching等人[34]在超声乳化术后2、4和8周时得到了相反的结果，即视网膜厚度减少(分别为-14、-9和-13μm)。他们认为，这可能是由于晶状体混浊和术后光学介质透明度恢复所导致的OCT测量误差。我们在对照组得到了类似的视网膜厚度减少的结果。应该记住的是，恢复光学介质透明度对OCT结果的影响可能会导致低估其在其他组中的实际增厚。

多项研究表明，单纯性白内障患者在术后12周和3个月滴注非淄体类抗炎药视网膜中央厚度最大程度的增加（达10.2μm）并在6个月时没有恢复到基线值[35-37]。这些研究的作者认为，在术后，使用NSAIDs减缓了视网膜增厚的速度。在我们的研究中，对照组患者术后视网膜中心厚度在2周后下降（-15μm，为基线值的0.05%），然后逐渐向基线值恢复，但未达到基线值；2个月后，与基线值的平均差异为-11μm，6个月后为-7.7μm（见表4，5，图1，2）。

关于应用NSAIDs预防和治疗CME的报道很多[16,38]，但在单纯性白内障超声乳化术后使用NSAIDs与类固醇滴注预防CME的额外好处，长期以来一直是一个未解决的问题。然而，在2018年PREMED研究中，0.09%溴芬酸被证明对预防CME有效[39]。

我们的研究结果显示，应用PGAs的患者在单纯性白内障超声乳化术后滴注NSAIDs会加速视网膜恢复到初始厚度。

结论

应用前列腺素类似物的POAG患者超声乳化术加植入IOL 6个月后，没有发现PCME。

术后应用非甾体抗炎药眼药水可以降低视网膜增厚的幅度，加速其恢复到基线值。

成功的单纯性白内障超声乳化术中，在没有增加CME可能性的全身和局部因素的情况下，即使在应用PGA的背景下，术后给予滴眼液形式的NSAIDs也不是必须的。

附加信息

利益冲突。作者声明与本文的发表没有明显或潜在的利益冲突。

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