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【应用研究】

户外活动和0.1 g·L^{-1}阿托品对学龄期儿童控制近视发展的疗效对比△

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Comparison of outdoor activities and 0.1 g·L^{-1} atropine in preventing myopia progression in children

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【Abstract】 **Objective** To compare the effects of outdoor activities and 0.1 g·L^{-1} atropine on prevention of myopia progression in school-age children. **Methods** A total of 180 myopic children aged 7-13 years (360 eyes) were selected from the ophthalmological clinic of Wenzhou People's Hospital from 2015 to 2017. They were randomly divided into 3 groups: the atropine group, the outdoor activity group and the control group. Children in the atropine group were given 0.1 g·L^{-1} atropine eye drops before bedtime every evening, one drop at one time, which was implemented by parents. The 0.1 g·L^{-1} atropine eye drops were diluted by 1.25 g·L^{-1} atropine eye drops and Tears Naturale eye drops according to the standard proportion; Children in the outdoor activity group were urged by the teachers and parents for outdoor activities during all class recesses and one hour after school; Children in the control group were without any treatment during this period. The time of follow-up was 1 year. The changes of myopia diopter, eye axis length and intraocular pressure (IOP) of the 3 groups of individuals before and after 1 year of intervention were examined and compared. The rapid growth rate of myopia diopter and the adverse reaction were recorded, and the differences were analyzed and compared. **Results** After 1 year of follow-up, the diopter changes in the 3 groups were statistically significant ($F = 291.39$, $P < 0.001$); further comparison in pairs: there was no significant difference in diopter change between the atropine group and the outdoor activity group ($q = 1.21$, $P > 0.05$); The diopter changes in the atropine group and the outdoor activity group were smaller than the control group, and the differences were statistically significant (both $P < 0.01$). The rapid growth rate of myopia was 44.17% (53/120) in the control group, 12.50% (15/120) in the atropine group and 14.17% (17/120) in the outdoor activity group. There was no significant difference in the rapid growth rate of myopia between atropine group and outdoor activity group ($P = 0.704$); The rapid growth rate of myopia between the atropine group and the outdoor activity group was lower than control group, and the differences were statistically significant (both $P < 0.017$). After 1 year of follow-up, the eye axis changes in the 3 groups were statistically significant ($F = 216.13$, $P < 0.001$); Further comparison in pairs: there was no significant difference in the eye axis change between the atropine group and the outdoor activity group ($P > 0.05$); The eye axis changes in the atropine group and the outdoor activity group were smaller than the control group, and the differences were statistically significant (both $P < 0.001$). The change of IOP in the control group was (-0.23 ± 4.17) mmHg (1 kPa = 7.5 mmHg), the atropine group was (0.25 ± 3.81) mmHg, and the outdoor activity group was (0.33 ± 3.72) mmHg, there were no significant differences ($F = 0.72$, $P = 0.487$). All individuals in the atropine group had no intolerable side effects. **Conclusion** Topical administration of 0.1 g·L^{-1} atropine eye drops and increasing outdoor time can effectively control eye axis length and myopia diopter, and there is no significant difference between the two groups in preventing of myopia progression in school-age children.

【Key words】 myopia; atropine; outdoor activity; children

【摘要】 **目的** 对比并分析户外活动和0.1 g·L^{-1}阿托品对学龄期儿童控制近视发展的疗效。**方法** 选取2015年至2017年温州市人民医院眼科门诊收治的7~13岁近视小学生共计180例(360眼)为研究对象,随机平均分成3组:阿托品组、户外活动组和对照组。阿托品组儿童每晚睡前滴一次0.1 g·L^{-1}阿托品滴眼液,一次一滴,由家长实施。0.1 g·L^{-1}阿托品滴眼液由1.25 g·L^{-1}阿托品滴眼液与新泪然滴眼液按标准比例稀释而成。户外活动组嘱托老师和家长督促儿童课间及下午放学后在户外自由活动至少1 h;对照组儿童这期间不做任何处理。随访时间为1 a。检查3组对象在干预前和干预1 a后的近视屈光度、眼轴、眼压变化,记录近视度数快速增长率及有无发生不良反应,进行分析并比较各组差异。**结果** 干预1 a后,3组的屈光度改变量差异有统计学意义($F = 291.39$, $P < 0.001$);进一步两两比较:阿托品组与户外活动组屈光度改变量差异无统计学意

义($q=1.21$,$P>0.05$);阿托品组和户外活动组屈光度改变量均小于对照组,差异均有统计学意义(均为$P<0.01$)。对照组近视度数快速增长率为44.17%(53/120),阿托品组为12.50%(15/120),户外活动组为14.17%(17/120)。阿托品组与户外活动组的近视度数快速增长率差异无统计学意义($P=0.704$);阿托品组和户外活动组近视度数快速增长率均小于对照组,差异均有统计学意义(均为$P<0.017$)。干预1 a后,3组的眼轴改变量差异有统计学意义($F=216.13$,$P<0.001$);进一步两两比较:阿托品组与户外活动组的眼轴改变量差异无统计学意义($P>0.05$),阿托品组和户外活动组眼轴改变量均小于对照组,差异均有统计学意义(均为$P<0.001$)。对照组眼压改变量为(-0.23 ± 4.17)mmHg(1 kPa=7.5 mmHg),阿托品组为(0.25 ± 3.81)mmHg,户外活动组为(0.33 ± 3.72)mmHg,差异无统计学意义($F=0.72$,$P=0.487$)。阿托品组儿童自诉未出现不能耐受的副作用。**结论** 局部使用0.1 g·L^{-1}阿托品滴眼和增加户外时间能有效控制眼轴增长及近视度数增加,且两者在控制学龄期儿童近视进展的疗效无明显差异。

【关键词】 近视;阿托品;户外活动;儿童
【中图分类号】 R779.7

随着手机、平板电脑等电子设备广泛使用,近年来青少年儿童的近视患病率逐年上升[1]。近视一旦发生就不可逆转,随着近视进展易导致高度近视,常常伴有眼组织病理性或退化性改变,如黄斑出血、黄斑裂孔、视网膜劈裂、视网膜脱离等,严重影响患者视功能[2-3]。青少年为近视眼高发人群,通常几岁至十几岁为发病高峰[4]。近视发生的年龄越小,成年后发展成高度近视的可能性越大[5]。因此,青少年近视防治已成为我国乃至全球一项公共卫生问题,有效预防和控制近视的发生发展是医学界和教育体系所面临的一项艰巨且重要的任务。近年来低浓度阿托品在改善儿童近视进展中的作用日益受到人们的关注,同时多项流行病学研究亦发现增加户外活动可减缓近视的发生发展[6-7]。本研究为前瞻性随机对照试验,通过不同的干预措施,分析并比较0.1 g·L^{-1}阿托品和户外活动对学龄期儿童控制近视发展的有效性和安全性。

1 资料与方法

1.1 一般资料 选取2015年至2017年温州市人民医院眼科门诊收治的7~13岁近视小学生共计180例(360眼)为研究对象,随机平均分成3组:阿托品组、户外活动组和对照组。研究对象纳入标准:矫正视力≥5.0,均未行眼部手术,排除眼部器质性病变及双眼视功能异常,同时排除正在配戴角膜塑形镜、硬性角膜接触镜的学生,所有入选对象及其法定监护人对本次研究目的、意义和眼部检查过程均知情同意。本研究遵循赫尔辛基宣言,并获得温州市人民医院伦理委员会批准。

1.2 检查方法 记录所有儿童的一般信息,包括性别及年龄、屈光度、眼轴长度、眼压及父母是否患有近视眼的情况,正式调查前进行预试验,评估问卷可信度和记录的一致性及有效性。在使用睫状肌麻痹药之前行眼轴、眼压测量:使用眼科A/B超(天津索尔SW-2100型)测量眼轴长度,重复5次并取平均值;使用非接触式眼压计(日本Topcon株式会社)测量眼压,重复3次取平均值。散瞳验光:使用10 g·L^{-1}环喷托酯(美国Alcon公司)作为睫状肌麻痹药,每隔5 min滴眼1次,共3次,30 min后根据瞳孔对光反射情况判断睫状肌麻痹程度,待睫状肌麻痹时对光反射消失,瞳孔直径≥6 mm后,对所有儿童使用电脑验光仪(日本Topcon株式会社)检查,之后行主觉验光测得屈光度,将其换算成等效球镜度,等效球镜度=球镜度数+1/2柱镜度数。

1.3 干预措施及观察指标 阿托品组儿童每晚睡前滴一次0.1 g·L^{-1}阿托品滴眼液,一次一滴,由家长实施。0.1 g·L^{-1}阿托品滴眼液由1.25 g·L^{-1}阿托品滴眼液(台湾麦迪森医药公司)与新泪然滴眼液(美国Alcon公司)按标准比例稀释而成。户外活动组嘱托老师和家长督促儿童课间及下午放学后在户外自由活动至少1 h。对照组儿童这期间不做任何处理。学龄期儿童每天课间休息4次,每次15 min,每周课程包括两节体育课,故户外活动组每周户外暴露时间约14 h,阿托品组和对照组不干预户外活动时间,每周约3 h。对所有儿童定期门诊随访,进行系统的眼科检查及询问有无任何不适,观察并记录有无不良反应,进行安全性分析。1 a后按上述同样的检查方法测量眼轴、眼压和散瞳验光,同时记录各组儿童的眼轴长度、眼压、散瞳验光后屈光度及近视度数快速增长例数。设定近视眼的屈光范围,等效球镜度≤-0.75 D,近视度数快速增长定义为每年屈光度变化>-0.5 D[8]。3组间性别、年龄、眼压、父母一方或双方有无近视等一般情况比较,差异均无统计学意义(均为$P>0.05$)。

1.4 统计学分析 采取SPSS 17.0统计软件对数据进行处理,近视眼屈光度及眼轴的描述采用均数±标准差;采用单因素方差分析进行各组间比较,当差异有统计学意义时,两两比较采用SNK-q检验;采用卡方检验分析各组干预1 a后近视度数快速增长率;以$P<0.05$为差异有统计学意义。

2 结果

2.1 各组干预后屈光度情况 3组间初始屈光度差异无统计学意义($F=0.13$,$P=0.879$)。干预1 a后,3组的屈光度改变量差异有统计学意义($F=291.39$,$P<0.001$),进一步两两比较:阿托品组与户外活动组屈光度改变量差异无统计学意义($q=1.21$,$P>0.05$);阿托品组和户外活动组屈光度改变量均小于对照组,差异均有统计学意义(均为$P<0.01$)。见表1。

表1 干预前后3组屈光度的变化情况

组别	初始屈光度/D	干预后屈光度/D	屈光度改变量/D
对照组	-1.54±1.20	-2.22±1.48	-0.68±0.21
阿托品组	-1.62±1.18	-1.80±1.44	-0.18±0.15
户外活动组	-1.59±1.27	-1.79±1.52	-0.20±0.18
F 值	0.13	3.15	291.39
P 值	0.879	0.044	<0.001

屈光度改变量 > -0.5 D 的眼数,对照组53眼,近视度数快速增长率为44.17%(53/120);阿托品组15眼,近视度数快速增长率为12.50%(15/120);户外活动组17眼,近视度数快速增长率为14.17%(17/120)。阿托品组与户外活动组的近视度数快速增长率的差异无统计学意义(P = 0.704);阿托品组和户外活动组近视度数快速增长率均小于对照组,差异均有统计学意义(均为 P <0.017)。

2.2 各组干预后眼轴情况 3组初始眼轴差异无统计学意义(F = 0.06, P = 0.941)。干预1 a后,3组的眼轴改变量差异有统计学意义(F = 216.13, P < 0.001);进一步两两比较:阿托品组与户外活动组的眼轴改变量差异无统计学意义(P > 0.05),阿托品组和户外活动组眼轴改变量均小于对照组,差异均有统计学意义(均为 P <0.001)。见表2。

表2 干预前后3组眼轴的变化情况

组别	初始眼轴/mm	干预后眼轴/mm	眼轴改变量/mm
对照组	23.92±1.16	24.30±0.85	0.38±0.13
阿托品组	23.94±1.07	24.05±0.76	0.11±0.08
户外活动组	23.89±1.11	24.02±0.82	0.13±0.12
F 值	0.06	4.31	216.13
P 值	0.941	0.014	<0.001

2.3 各组干预后眼压情况 干预1 a后,对照组眼压为(14.92±3.11)mmHg(1 kPa = 7.5 mmHg)、阿托品组为(14.87±2.98)mmHg、户外活动组为(15.07±2.89)mmHg,3组间眼压差异无统计学意义(F = 0.14, P = 0.865);对照组眼压改变量为(-0.23±4.17)mmHg,阿托品组为(0.25±3.81)mmHg,户外活动组为(0.33±3.72)mmHg,差异无统计学意义(F = 0.72, P = 0.487)。

2.4 药物副作用 阿托品组儿童使用0.1 g·L^{-1}阿托品滴眼液后在随访的1 a中主诉均未发生如口干、皮肤过敏、发烧、心悸及面部发红等全身反应,同时眼科常规检查未出现眼睑过敏反应,局部刺激、充血肿大、滤泡性结膜炎,白天未有明显畏光和近距离视物模糊现象。

3 讨论

当前青少年的户外时间逐步被室内时间代替,导致低龄化近视发生率逐年上升。如何阻止眼轴过快增长,如何有效预防及控制近视一直是国内外眼科研究人员关注的焦点。阿托品滴眼液是目前唯一被大量研究证明能长期持续控制近视进展的药物[9]。高浓度的阿托品(10 g·L^{-1}、5 g·L^{-1})滴眼液控制近视进展效果更好,但是其具有一定局限性,试验者不容易耐受,易出现畏光、阅读困难、头痛等副作用,依从性差[10]。Chia等[11]发现应用0.1 g·L^{-1}、2.5 g·L^{-1}、5.0 g·L^{-1}阿托品滴眼液2 a,控制近视进展程度的差异无统计学意义,但0.1 g·L^{-1}阿托品的副作用却是最小的,而且3组停药后,0.1 g·L^{-1}阿托品组的近视进展度数反弹最小[12]。关于阿托品控制近视的机制目前并没有明确的结论。过去研究认为阿托品通过对睫状肌上受体拮抗作用来麻痹睫状肌使其放松调节,产生调节麻痹而抑制近视发展[13]。目前关于阿托品抑制近视具体作用位点和机制有两种假设:(1)通过视网膜外的M受体途径作用,最有可能作用位点是巩膜上M受体[14-15],影响巩膜重塑进而抑制眼轴进展;(2)通过视网膜上M受体调控,Ashby等[16]研究发现玻璃体腔注射阿托品可阻止眼轴延长,抑制由实验性近视所引起的小鸡视网膜上胰高血糖素表达阳性的无长突细胞ZENK基因表达下降。

Mutti等[17]调查发现近视眼儿童每周平均户外时间7.4 h,正视眼儿童每周9.7 h,两者差异有统计学意义(P <0.001)。长时间户外活动与降低近视发生率相关(OR = 0.92, P = 0.005)。对比新加坡和中国儿童研究显示,中国组儿童近视发生率18.5%,明显低于新加坡组36.7%,其中中国儿童每周平均户外时间8.7 h,较新加坡组儿童每周平均3.3 h长很多,差异有统计学意义(P <0.001)[18]。增加户外活动时间对近视的发生有抑制作用,还可能最大限度减少长时间近距离工作和父母近视等危险因素带来的近视风险。关于户外活动相较于室内活动能抑制近视的原因国内外研究人员提出各种假说。户外高光照度的环境促进人体皮肤合成维生素D并影响视黄酸这一信号分子的调节作用[19]。维生素D具有强大的调节细胞分化、抗癌及抗增殖作用,因此可能是维生素D直接作用于巩膜产生抗增殖作用[20],延缓眼轴增长和屈光度改变。近视发生过程中眼内神经递质变化起着重要作用,多巴胺不仅是参与视网膜各层神经元之间视觉信息传递的神经递质,也是视网膜时钟网络重要组成部分[21],高光照强度能提高视网膜多巴胺的分泌水平,产生信号,抑制眼轴生长,趋向正视化[22]。

本研究采取不同干预措施实行前瞻性对照研究发现,阿托品组与户外活动组屈光度改变量差异无统计学意义(P >0.05);阿托品组和户外活动组屈光度改变量均小于对照组,差异均有统计学意义(均为 P <0.01)。阿托品组与户外活动组近视度数快速增长率的差异无统计学意义(P = 0.704);阿托品组和户外活动组近视度数快速增长率均小于对照组,差异均有统计学意义(均为 P <0.017)。3组间眼压改变量差异无统计学意义(P = 0.487),可见0.1 g·

L^{-1}阿托品滴眼不易引起眼压升高。上述结果表明，0.1 g·L^{-1}阿托品和增加户外时间都可以安全有效控制近视度数的进展。屈光度和眼轴长度存在显著相关性，在青少年近视中，轴性近视是主要原因[23]。眼轴的不断延长导致眼球后极部的血液循环发生障碍，引起后端脉络膜的慢性损伤，逐渐发生退行性病变即高度近视性视网膜病变[24]，因此是否控制近视患者的眼轴增长成为评价能否有效控制近视发生发展的主要指标。本研究发现干预1 a后，阿托品组与户外活动组眼轴改变量差异无统计学意义（$P>0.05$）。阿托品组和户外活动组眼轴改变量均小于对照组，差异均有统计学意义（均为$P<0.001$）。这证实0.1 g·L^{-1}阿托品及增加户外时间能明显延缓眼轴增长，从而控制儿童近视的发展。

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