**Hyperopic Reserve as an Indicator of Myopia Prevention by Atropine (LAMP2 Study)**

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The Low-concentration Atropine for Myopia Prevention (LAMP2) study has shown that 0.05% atropine eye drops can delay the onset of myopia by 47% over 2 years.1 However, not all children are at equal risk of developing myopia, and therefore a targeted approach to minimize unnecessary treatment for those who will not develop myopia is needed. To address this research gap, we evaluate factors associated with the efficacy of low-concentration atropine in delaying myopia onset to identify whom will benefit from this prophylactic intervention. It is a secondary analysis of the LAMP2 study, a randomized, placebo-controlled, double-masked trial, and was approved by the Ethics Committee of the Hong Kong Eye Hospital and adhered to the tenets of the Declaration of Helsinki.

The participants who completed 2-year follow-up in LAMP2 study were included. In the original LAMP2 study, participants were non-myopic children aged 4–9 years with cycloplegic spherical equivalent (SE) between +1.00–0.00 D, who were randomized into groups that received 0.05%, or 0.01% atropine or placebo eye drops once nightly in both eyes. Cycloplegic autorefraction was performed using a Nidek ARK-510A autorefractor unit following the cycloplegia regimen of 1% cyclopentolate (Cyclogyl, Alcon-Convreur, Rijksweg, Belgium) and 1% tropicamide (Santen, Osaka, Japan).2 Axial length (AL) was measured on a Zeiss IOL Master 700 (Carl Zeiss Meditec Inc., Dublin, CA). Myopia was defined as cycloplegic SE refraction of at least -0.50 D in either eye.2 The outcome measures included: (1) factors associated with myopia onset, SE progression, and AL elongation over 2 years, and (2) the SE progression and AL elongation over 2 years in various baseline hyperopic reserve. Factors evaluated included: (1) age at treatment, (2) sex, (3) baseline hyperopic reserve, (4) parental myopia, (5) baseline outdoor time, (6) baseline near work and (7) compliance.

A total of 353 (74.5%) participants completed the 2-year follow-up (Table S1). Over 2 years, low baseline hyperopic reserve and high level of parental myopia increased the risk of myopia onset (OR=0.02, P<0.001 and OR=2.29, P=0.003 respectively), SE progression (β=0.45, P<0.001 and β=-0.22, P=0.003 respectively) and AL elongation (β=-0.22, P<0.001 and β=0.08, P=0.01 respectively) (Table S2). Younger age was associated with AL elongation (β=-0.08, P<0.001), but not SE progression nor myopia onset. Interaction effect on both SE progression (P=0.02) and AL elongation (P=0.02) was detected between baseline hyperopic reserve and 0.05% atropine treatment, but not with 0.01% atropine. There was no interaction of atropine treatment with parental myopia nor with age (Table S2).

To further elaborate the interaction effect, subgroup analysis found that in 0.05% atropine group, the SE progression over 2 years was similar across groups with various baseline hyperopic reserve. However, in the 0.01% atropine and placebo groups, the SE progression was affected by the baseline hyperopic reserve, with the lesser baseline hyperopic reserve the faster the progression (P-trend<0.001 in both groups). Similar trends were observed for AL elongation (Figure 1, Table S3). That indicates 0.05% atropine is more effective than 0.01% or placebo for eyes with less hyperopic reserve.

Among participants with the baseline hyperopic reserve of less than +0.75 D, the SE progression over 2 years was less in 0.05% atropine than that in placebo (adjusted differences from 0.55 D to 0.92 D, P values<0.001) and in 0.01% atropine group (adjusted differences from 0.45 D to 0.69 D, P values<0.01). Among participants with the baseline hyperopic reserve between +1.0 D and +0.75 D, the SE progression had no significant difference among all treatment groups. Similar relationships were observed in AL elongation over 2 years (Table S3).

The participant dropout rate was higher than anticipated mainly due to emigration, the loss of contact or unwillingness to complete ocular examinations during COVID-19 pandemic, which could potentially hamper the statistical power and lead to bias. Furthermore, 14 participants (11.6%, 14/121) discontinued the study to switch to other treatments after their myopia progressed. Nevertheless, the participants who completed 2 years and those who did not are comparable (Table S1). The dropout rate was not related to treatment groups or SE progression. Previous sensitivity analyses suggested that dropouts did not affect the main results.1 Second, this study was confined to participants with a narrow range of baseline hyperopic reserve, from 0 D to +1.0 D, specifically focused on the group of premyopic children. Treatment efficacy in participants with baseline hyperopic reserve more than +1.0 D had not been evaluated. Third, the hyperopic reserve of +0.75D may serve as a potential cutoff for 0.05% atropine as prophylactic treatment. Consistently, children with < +0.75 D of hyperopia were also found with an increased risk for developing myopia.3 However, the limited sample size in subgroup analysis may reduce statistical power, and therefore further studies with a larger sample size are warranted. Fourth, younger age was only found as risk factor for axial elongation, but not for myopia onset nor SE progression. In addition, subgroup analysis stratified by age showed that the younger age the faster AL elongation in all treatment groups, but not with SE progression in the 0.05% or 0.01% atropine group. (Table S3) This could be again attributed to the limited sample size.

Consistent with previous studies, 4-6 children with less hyperopic reserve and high level of parental myopia were at a higher risk to develop myopia. Preventive treatment with low-concentration atropine should be targeted to them. While starting low-concentration atropine in eyes with preserved hyperopic reserve would likely result in a lower likelihood of progressing to myopia, 0.05% atropine is more effective than 0.01% or placebo for eyes with less hyperopic reserve.

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