Atropine and Ocular Hypotensives in The Control of Myopia.

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Research Article

Keywords: myopia, atropine, ocular hypotensives, ametropia.

Posted Date: September 13th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-719191/v1

Abstract

Purpose

To describe the results of topical atropine 1% weekly combined with a fixed combination of ocular hypotensives (dorzolamide + timolol), versus ocular hypotensives alone, in children and adolescents.

Methods

A retrospective review of medical records of myopic children and adolescents from September 2003 to June of 2019. The unit of analysis of the data was the change in the magnitude of myopia in a given eye between two consecutive visits (CMCV) and were divided in three groups: “non-adherent”, “hypotensive” and “atropine”, and classified according to the magnitude of myopia progression.

Results

There were statistically significant differences in the percentages of the CMVC analysis units included in the “completely controlled myopia” classification (higher for the “Atropine” group) and in the “moderate progression” and “severe progression” classifications (lower for the “Atropine” group). Mean progression rate of the CMCV analysis units included in the “atropine” group was significantly lower (-0.13 ± 0.41 Diopters/year) than in the “hypotensives” group (-0.41 ± 0.54 Diopters/year), and in the “non-adherent” group (-0.59 ± 0.57 Diopters/year).

Conclusions

In a group of myopic children and adolescents in Colombia during the periods of time in which they received 1% atropine, one drop weekly, in combination with dorzolamide + timolol, every 12 hours, showed better control of the progression of myopia, than in the time periods in which they received only ocular hypotensives or were not adherent to pharmacological treatment. Further research is warranted.

Introduction

The use of topical atropine in cases of myopia began to be explored in the second half of the 19th century, when it was used mainly in accommodation spasm related to myopia, but soon the researchers began to notice that it also seemed to stabilize the progression of myopia [1, 2]. Since Kepler's observations at the beginning of the 17th century, accommodation had been linked to myopia, and therefore it was thought even until the late 20th century that an accommodation-related mechanism explained the effect of atropine in the control of myopia [2–4]. However, various groups of researchers in the 1990s found that atropine decreased axial growth related to experimental form deprivation myopia in chickens, although these animals do not have muscarinic receptors in the ciliary body and therefore

atropine does not block accommodation in them [5, 6]. This eliminated accommodation as a possible mechanism for the anti-myopia effect of this anticholinergic. Despite multiple experimental studies, the exact mechanism of topical atropine in its already demonstrated myopia control effect is not yet known, but it ultimately appears to be multifaceted and rather complex [2, 7–10].

On the other hand, there is much discussion about the effect of ocular hypotensives in the control of myopia, and there is no clear evidence from clinical studies to support this. Only a couple of studies with small samples, and medium-term follow-up, conducted in the 1980s, suggested that they could have a positive effect [11, 12]. However, in another study published by Jensen in 1991, the results did not favor the use of timolol to control the progression of myopia [13]. Though, due to the excellent preliminary results that Galvis et al. observed with the combination of atropine 1%, one drop weekly, and ocular hypotensives, in their 2012 publication they considered that it could be possible that there was some type of synergy between these two types of medications [14]. Some recent experimental studies also reinforce the possibility of a positive effect of some ocular hypotensives in myopia, although its mechanism is not entirely clear, nor if the decrease in intraocular pressure is related to this effect [15–17].

In the present study, a retrospective analysis of the results of the use of topical hypotensive drugs is carried out and it is compared with the effect of the combination of atropine 1% one drop weekly and ocular hypotensives, or not receiving pharmacological treatment, in a group of children and adolescents with diagnosis of myopia or myopic astigmatism in Colombia.

Materials And Methods

This was a retrospective cohort study. The population consisted of patients between 4 and 19 years of age with a diagnosis of myopia or myopic astigmatism and with prescription by the treating ophthalmologist to receive pharmacological management in order to limit its progression, either with only a fixed combination of ocular hypotensives (dorzolamide + timolol) or with a combined treatment of fixed combination of hypotensive, plus 1% atropine once weekly.

The data were extracted from an anonymized database obtained from the clinical records of the Virgilio Galvis Ophthalmology Center, of myopic patients treated between September 2003 and June 2019, and who had a record of at least two follow-up visits, with at least six months difference between them.

The same patient could have received different types of treatment during that period of time, and also at the time of the questioning in the control visits, he or she was asked about the compliance with the treatment during the period of time since the previous control and it could be determined if the patient had no adherence during that time (if the patient reported that the treatment had been applied less than 25% of the time). Then, it was decided to determine as the unit of analysis of the data the change in the magnitude of myopia in a given eye between two consecutive visits (CMCV), which had a period of time of at least 6 months between them, and it was classified this observation associating it with the treatment received during said period. That is, a single patient throughout his controls, was able to generate multiple CMCV analysis units.

In general, until October 2009, myopic patients were treated only with ocular hypotensives, between November 2009 and October 2011 some received hypotensives and other hypotensives plus atropine, and since November 2011 all patients were treated with hypotensives plus atropine.

These CMCV units of analysis, as mentioned, were then divided into groups according to the treatment received during that specific time period. CMCV were classified within the group called “hypotensives”, if in the period immediately prior to the control visit the patient had applied Dorzolamide + Timolol eye drops every 12 hours permanently (that is, more than 75% of the time) in both eyes. CMCV were classified within the group called “atropine” if in the period immediately prior to the control visit the patient had permanently applied Dorzolamide + Timolol every 12 hours in both eyes and additionally had applied 1% Atropine, a weekly drop in both eyes (more than 75% of the time). Finally, CMCV were classified within the group called “non-adherent” if in the period immediately prior to the control visit the patient reported having applied the treatment less than 25% of the time during that period. CMCV units of analysis in which the patient was unclear as to how long the treatment had or had not been applied, or whether had applied it 25–75% of the time, were excluded from the study.

A descriptive analysis was carried out for the quantitative variables with the mean and standard deviation, and for the qualitative variables with the relative frequencies and absolute frequencies.

The progression of myopia was calculated in each time period by means of the difference of the spherical equivalent between the two visits divided in the follow-up time in years and fractions of a year, thus giving a diopter/year rate (D/year).

This diopter/year rate was categorized according to the myopia progression criterion as “mild progression” (progression < 0.50 D per year), “moderate progression” (progression between 0.50 and 1.00 D, per year) and “severe progression” (progression greater than 1.00 D per year) [18]. Additionally, a subgroup of "completely controlled myopia" was considered, which included eyes with zero progression, that is, equal to or less than 0.00 D per year. The relative frequency presented in each treatment group was determined according to the myopia progression categorization.

A bivariate analysis was performed evaluating the relationship between the three different treatment groups of the CMCV analysis units, that is: "hypotensive", "atropine" and "non-adherent", and the diopter/year rate (Anova test with robust variance of a linear regression for continuous variables and a chi-square test for categorical variables).

The Hazard ratio was estimated to compare the CMCV units of analysis in the three treatment groups, using the “non-adherent” group set as the base category.

For the statistical analysis, an alpha of 0.05 was used and the IBM SPSS Statistics program for Windows, version 25.0 was used.

Results

In total, 436 CMCV analysis units were included, of eyes diagnosed with myopia or myopic astigmatism, from 74 eyes of 37 patients, who were followed on average for 7.42 ± 2.36 years (range 2.02 to 13.75 years). 30% (n = 11) of the patients contributed information to the three groups of CMCV analysis units (“hypotensive”, “atropine” and “non-adherent”); 59% (n = 22) of the patients contributed information to two groups of analysis units and 11% (n = 4) of the patients contributed information to only one group of analysis units. On average, the number of CMCV analysis units generated per patient, taking into account both eyes, was 11.78 ± 4.10.

Of the 436 units of analysis, 21.10% (n = 92) were from the “non-adherent” group; 33.49% (n = 146) belonged to the "hypotensive" group, and 45.41% (n = 198) belonged to the "atropine" group.

The duration between the initial and final controls of each CMCV analysis unit averaged 1.32 ± 0.72 years. The CMCV unit of analysis with the shortest time between the two follow-up controls was 0.51 years and the longest between the two controls was 5.83 years. The average age of the patients to whom the CMCV units of analysis corresponded, taking into account all the 436 analyzed, was 13.95 ± 3.31 years.

For the 92 CMCV units of analysis, provided by 25 of the 37 patients, which were included in the “non-adherent” group, at the time of each evaluation, the patients had an average age of 14.52 ± 3.03 years, with a minimum age of 7.78 years and a maximum age of 18.41 years. For the 146 CMCV analysis units, provided by 28 of the 37 patients, which were included in the “Hypotensive” group, at the time of each evaluation, the patients had an average age of 12.53 ± 3.35 years, with a minimum age of 4.42 years and a maximum age of 18.98 years. For the 198 CMVC units of analysis, provided by 28 of the 37 patients, which were included in the “Atropine” group, at the time of each evaluation, the patients had an average age of 14.74 ± 3.08 years, with a minimum age of 6.46 years and a maximum age of 20.31 years. There was no significant difference between the mean ages of the patients to whom the CMCV units of analysis included in each of the three groups corresponded [F = 3.63 (P = 0.057)].

60.60% of the CMCV analysis units analyzed corresponded to women. Other characteristics of each group can be observed in Table 1.

The percentage of CMCV units of analysis that, in each group, presented “completely controlled myopia” (that is, progression values equal to or less than 0.00 diopters/year), “mild progression” (progression < 0.50 D per year), “moderate progression” (progression between 0.50 and 1.00 D, per year) and “severe progression” (progression greater than 1.00 D per year) of myopia, are shown in Fig. 1. There were statistically significant differences in the percentages of the CMVC analysis units included in the “completely controlled myopia” classification (higher for the “Atropine” group) and in the “moderate progression” and “severe progression” classifications (lower for the “Atropine” group).

When making comparisons of the classification of myopia progression of the CMCV units of analysis individually directly between the three different groups, it was evidenced that “completely controlled myopia” showed a significantly higher result in the CMCV units of analysis of the group of “atropine”

compared to the “non-adherent” group. [HR = 4.00 (95% CI 2.38–7.72) P = 0.001] and also in comparison with the “Hypotensives” group [HR = 3.05 (95% CI 2.13–4.39) P = 0.001]. On the contrary, there was no statistically significant difference between the “hypotensives” and the “non-adherent” groups in terms of CMCV units of analysis classified according to progression (Table 2).

Regarding the average progression rate of the CMCV analysis units included in each group, in the “non-adherent” group it was − 0.59 ± 0.57 D/year; in the “hypotensives” group it was − 0.41 ± 0.54 D/year, in the “atropine” group it was − 0.13 ± 0.41 D/year. In the Anova it was found that there was a statistically significant difference in the D/year rate with respect to the three treatment groups [F = 60.4 (P = < 0.001)].

Discussion

Some researchers, fundamentally thinking that they were acting in the control of accommodation, continued to use atropine for the control of myopia during the early 20th century, which had already begun to be used in myopic patients 4 or 5 decades earlier. Pollock approximately between 1910 and 1915, was the first to use it for long periods of time for the treatment of myopia (for a duration of several months to almost a year). The therapy also required myopic schoolchildren to avoid near work (reading and writing), with the difficulties that this entailed in education [1]. In the following four decades of the 20th century, the pharmacological treatment of myopia was practically abandoned to a large extent, or at least that is what the scarcity of publications on the matter in that period of time suggests [19, 20]. In the 1960s there appeared to be a resurgence of interest in the subject [21–24], but despite the evidence of the effectiveness of atropine treatment, even until the late 20th century this alternative was not popular among ophthalmologists in the Western Hemisphere and it had notable detractors [25–27]. Finally, a compelling body of evidence has emerged over the past 20 years, including very well-designed studies, conducted primarily in Asia, demonstrating the efficacy and safety of the use of topical atropine in the management of myopia in children, which has been proven in various meta-analysis, being in general more effective, however, atropine used at higher concentrations (0.5 or 1.0% daily), but which has the disadvantage of tolerance due to the effects on the pupil and blockage. of accommodation [2, 18, 28–35]. Both the concentration and the frequency of atropine have been modified in several studies in order to minimize the side effects, while trying to preserve the beneficial effects. As early as 1999 it had been suggested that because daily drops between 0.05% and 0.25% atropine were well tolerated, these concentrations could be used initially to control the progression of myopia in certain children [28]. In 2012, the results of the Atropine for the Treatment of Myopia 2 (ATOM 2) study indicated that the efficacy of an atropine at an extremely low concentration (0.01%) applied once daily at night for the control of the progression of the myopia, had minimal side effects and after 2 years of treatment and 1 year of suspension, the most diluted atropine turned out to be the most effective, basically because it had a lower rebound effect, than the higher concentrations [18]. However, as noted by Galvis et al., when in the ATOM 2 study considered children who received 0.1% atropine or 0.01% atropine compared to those who received the highest concentration (0.5% atropine), there were significant differences in progression during the first year of treatment, since a slower progression was observed in the 0.5% atropine group [36]. The ATOM 2 study did not include the direct comparison of a dilute atropine group versus a control

group, so Yam et al. designed the LAMP study (Low-concentration Atropine for Myopia Progression) whose initial results were published in 2019. They found that atropine diluted to 0.01% decreased axial length growth by only 12%, compared to the placebo group, and this difference did not reach statistical significance. The authors of the LAMP study suggested that 0.05% atropine was the most effective among the dilutions studied, in controlling the progression of myopia and elongation of axial length during 1 year of treatment, and was maintained as well tolerated [33]. The authors of the LAMP study recently reported the results at 2 years of follow-up. The efficacy of atropine at 0.05% observed with this observation period was double that observed with atropine at 0.01%, and it remained the optimal concentration among the concentrations of diluted atropine studied in the slowing of the progression of the disease. myopia [34–35]. While Yam et al. found all low-concentration atropine (0.05%, 0.025%, and 0.01%) were well tolerated [33], recently Joachimsen et al. in a small group of Caucasian children found more frequent and severe symptoms than in a previous study by the same authors with 0.01% atropine [37, 38].

A different approach has been not to reduce the concentration of atropine, but its frequency of application, taking into account the long half-life of atropine, and inter-daily, weekly and even, recently, monthly doses have been reported [14, 29, 39]. In 2012, Galvis et al. suggested that applying a 1.0% drop of atropine each week, rather than a daily dose, would facilitate adherence in young patients. In their study, they used atropine together with progressive multifocal glasses with a photochromic filter and also hypotensive eye drops. Treatment tolerance was good and treatment was very effective in stopping the progression of myopia in a preliminary study with a group of 33 patients with one year of follow-up [14]. Hypotensive drugs have been used by some researchers for decades in the control of myopia, with the idea that lowering intraocular pressure decreases a stimulus for the growing of axial length [11–13]. However, the evidence for this effect in humans is very poor, and in fact in a study published in 1991 including 142 children, the results did not favor the use of timolol to control the progression of myopia. After two years, myopia increased by -0.59 D/year in the timolol group, compared with − 0.57 D/year in the control group [13].

However, in experimental studies in guinea pigs, an ocular hypotensive (latanoprost) was recently found to significantly slow the progression of myopia [15, 16]. Furthermore, brimonidine has also shown an effect in the experimental inhibition of form-deprivation myopia [17]. It is not yet clear what are the mechanisms of action in its anti-myopia effect.

In the patients included in the present study, hypotensive drugs were used either alone (dorzolamide + timolol every 12 hours) or combined with 1% atropine one drop weekly. To perform the analysis of the results, as already explained, the observation periods of at least 6 months for each eye were considered as the CMCV units of analysis. The percentages of CMCV units of analysis classified as “completely controlled myopia” were higher, with a statistically significant difference, in the eyes that during the periods analyzed received 1% atropine one drop per week plus ocular hypotensives every 12 hours, versus the other two groups. analyzed, that is, those eyes that did not receive any pharmacological treatment during the analyzed period (“non-adherent” group) and those that only received dorzolamide + timolol

(“hypotensives” group). The hazard ratios reached very important values: when comparing the “atropine” group versus the “non-adherent” group it was 4.00 (95% CI 2.38–7.72) and when comparing it with the “hypotensives” group it was 3.05 (95% CI 2.13–4.39). This can be interpreted as that in a given period, an eye within the “atropine” group was 4 times more likely to have complete control of progression, compared to an eye within the “non-adherent” group, and approximately 3 times more likely than one in the "hypotensives" group. Analyzing the behavior of the CMCV units of analysis in each classification of myopia progression, and considering that there were no significant differences between the three groups (“non-adherent”, “atropine” and “hypotensives”) in the classification of "mild progression" of myopia, but a significant difference did appear in that of "moderate progression", the percentage of this last classification being lower in the group of "atropine", it would seem then that a large percentage of these eyes with "moderate progression" were those that presented minor progressions, eventually increasing the percentage of eyes with “completely controlled myopia”.

On the other hand, the percentages of CMCV units of analysis classified according to the progression of myopia did not reach significant differences between the “non-adherent” and “hypotensives” groups, which does not reinforce that the use of dorzolamide + timolol alone, have any significant effect in controlling the progression of myopia.

A statistically significant difference was also found between the progression rate of the CMCV units of analysis in periods in which the eyes were treated with 1% atropine weekly plus ocular hypotensives (-0.13 ± 0.41 D/year) versus the others two groups (“non-adherent” group = -0.59 ± 0.57 D/year and “hypotensives” group = -0.41 ± 0.54 D/year). This reinforces the possibility that the “atropine” group ultimately had greater control of myopia progression.

The methodology given to the analysis of the cases in the present study, in which the change in the magnitude of myopia in a given eye between two consecutive visits (CMCV) was considered as the unit of analysis, does not allow a direct comparison with the findings of other studies in which continuous follow-up periods of the patients were analyzed. This latter approach was not considered adequate in the present study because almost all the patients (89%) presented a change in medication or periods in which they reported non-adherence to treatment, during the time of follow-up. However, a rough comparison can be made with some of the results reported by other groups.

In the Atropine for the Treatment of Childhood Myopia (ATOM1) study, in the evaluation after one year, the mean progression of myopia in the eyes treated with placebo was − 0.76 ± 0.44 D, while in the group of children who received treatment with 1% atropine every night, there was a reduction in myopia by 0.03 ± 0.50 D [30]. On the other hand, in the ATOM2 study, the average progression after one year of treatment with 0.5% daily atropine was − 0.17 ± 0.47 D [18]. As a comparison in the LAMP study after 1 year of follow-up, the mean progression was − 0.27 ± 0.61 D in children who received atropine diluted 0.05% daily [33]. Taking into account the limitations of the direct comparison, as explained above, in any case the data of the mean progression found in the present study in the eyes that received atropine at 1% weekly plus ocular hypotensives (-0.13 ± 0.41 D/year) would seem to be located between what was achieved

with the use of 1% daily atropine in the ATOM1 study and that achieved with 0.5% daily atropine in the ATOM2 study, and it seems to be clearly better than the annual progression in the LAMP study with atropine daily at 0.05%.

Additionally, according to the data and the graph published in the ATOM1 and ATOM2 studies, it can be calculated that approximately 88.3% of the eyes of the children who received 1% atropine every night progressed < 0.50 D in one year. In the present study, 88.8% of the analysis units (that is, the change in the magnitude of myopia in a given eye between two consecutive visits, CMCV) in the eyes that during those periods received atropine 1% weekly + ocular hypotensives, progressed < 0.50 D in one year, a percentage slightly higher than that mentioned in the ATOM1 study, a clinical trial in which a much more frequent dose of 1% atropine was used (one drop every night). On the other hand, when comparing it with the percentages of eyes with progression < 0.50 D in one year using more diluted atropine, in the ATOM2 study, we found that these were much lower: the percentages of eyes that progressed less than 0.5 diopters in the first year were 50%, 58%, and 63% in the 0.01%, 0.1%, and 0.5% atropine groups, respectively [18].

In the LAMP study after one year of treatment, the percentages of eyes that progressed less than 0.5 D receiving diluted atropine at different concentrations were also lower (69.6%, 51.6% and 43.8% in the groups that received atropine at 0.05%, 0.025% and 0.01 %, respectively) [33].

In other words, the control of the progression of myopia achieved with the combination of atropine at 1% weekly and the use of ocular hypotensives, seems to be very similar to that achieved with atropine at 1% daily, and superior to that achieved with daily atropine in lower concentrations [18, 30, 33]. This leads us to wonder whether the concomitant use of ocular hypotensives (and specifically dorzolamide + timolol) has a possible synergistic effect on the effect of atropine in the control of myopia.

A weakness of the present study is that the axial length data could not be analyzed, since this measurement was performed only in a small percentage of the control visits. With all the recent evidence, this data has been indicated as very important in the follow-up of myopic patients in treatment [40–42]. Some investigators have suggested that the axial length of an eye can be calculated based on refraction and keratometry data [43], but such estimates have been shown to be inaccurate [44]. It is therefore essential to carry out the measurement with a biometer, preferably optical, of which there are multiple models available for clinical use today, which have been shown to be quite comparable [45]. Close monitoring of axial length is now included in our current protocol, at least once a year.

In conclusion, in a group of myopic children and adolescents in Colombia, it was found that during the periods of time in which they received 1% atropine, one dose a week, in combination with dorzolamide + timolol, every 12 hours, they presented better control of the progression of myopia, than in the time periods in which they received only ocular hypotensives or were not adherent to pharmacological treatment. Further studies are required to confirm if this beneficial effect is related only to the use of 1% atropine weekly, or if hypotensive substances add some efficacy to the effect of atropine.

Declarations

Funding No funding was received for this research.

Conflict of Interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Availability of data and material All data related to this study are available by request addressed to the corresponding author, with adequate justification from the requesting researcher.

Code availability Not applicable

Authors' contribution All authors attest that they meet the current ICMJE criteria or Authorship. VG, participated in the design of the study, interpretation of data, revision and edition of the manuscript. He was one of the two lead authors of the manuscript. AT participated in the design of the study, interpretation of data, was involved in drafting the manuscript, and revised and edited the manuscript. He was one of the two lead authors of the manuscript. JL was involved in checking the database for plausibility, made substantial contributions to interpretation of data and was involved in drafting the manuscript. CJR was involved in checking the database for plausibility, made substantial contributions to interpretation of data and was involved in drafting the manuscript. SES participated in the design of the study, interpretation of data, revision and edition of the manuscript. SJV participated in the design of the study, interpretation of data, was involved in drafting the manuscript and in the revision and edition of the manuscript. NFR was involved in checking the database for plausibility, made substantial contributions to interpretation of data and was involved in drafting the manuscript. JJR participated in the design of the study, interpretation of data, revision and edition of the manuscript. PAC participated in the design of the study, interpretation of data, revision and edition of the manuscript. Each author participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be responsible for all aspects of the study and publication in guaranteeing that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. In addition, all authors read and approved the final manuscript for publication.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional ethical committee Fundación Oftalmológica de Santander FOSCAL, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required. This article does not contain any studies with animals performed by any of the authors.

Consent for participation A secondary analysis of an anonymized database was performed, and in these cases the institutional ethics committee and local legislation do not require informed consent.

Consent for publication Not applicable.

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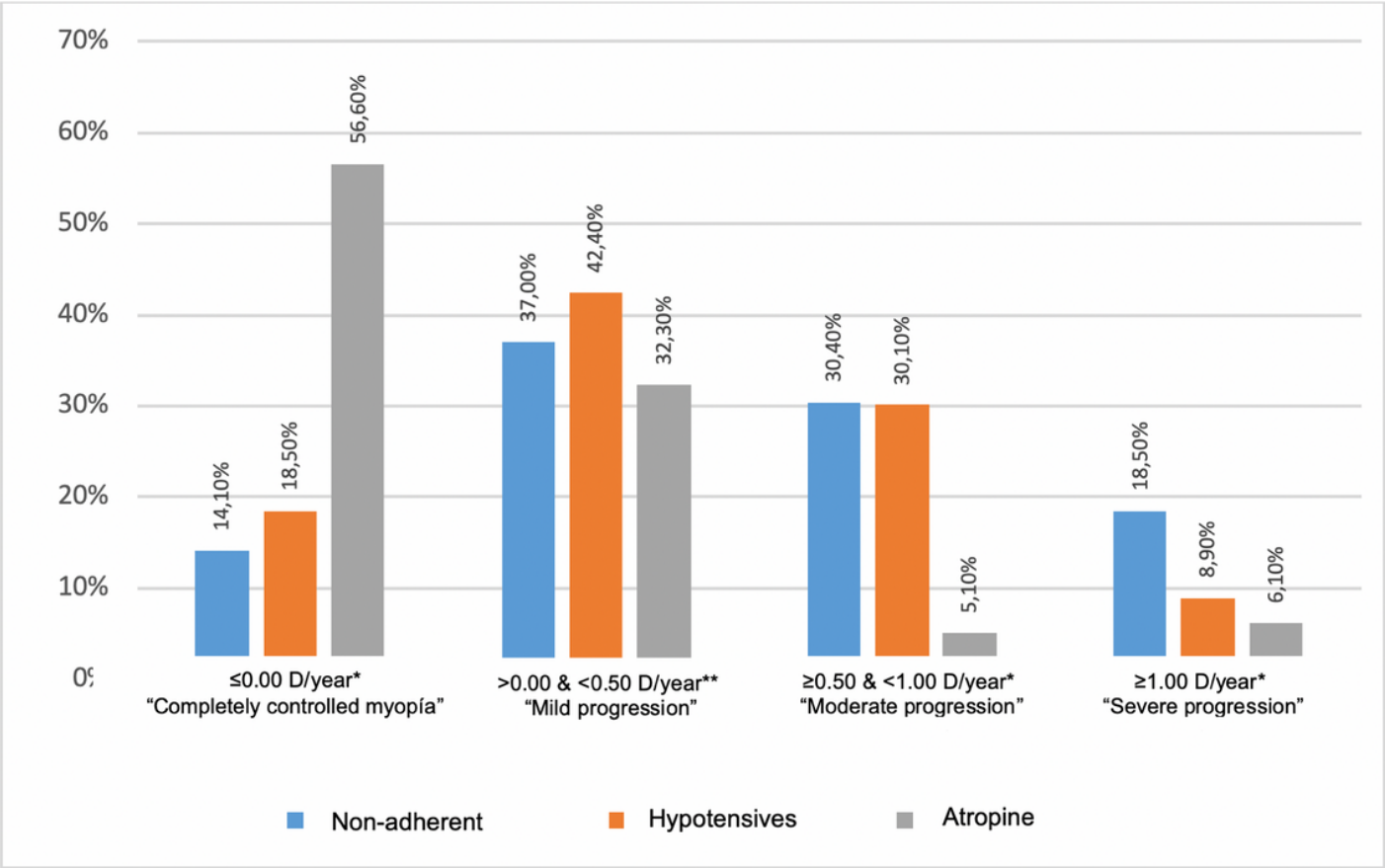
https://doi.org/10.1007/s10792-018-1006-z

Tables

Tables 1 and 2 are not available with this version.

Figures



* P-value <0.05
** P-value >0.15

Figure 1

Percentage of CMCV analysis units with “completely controlled myopia” or with “mild”, “moderate” or “severe myopia progression".