

Twice weekly atropine as a primary treatment for amblyopia: How does this compare with daily atropine?

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Abstract

Aim: This paper presents a service review giving results of twice weekly atropine treatment compared with daily treatment for amblyopia in a clinical setting and compares the results with our previous research.

Methods: In a retrospective case note review 70 patients treated with twice weekly atropine for amblyopia were compared with a previous cohort treated with daily atropine.

Results: Seventy patients were included in the data analysis for twice weekly treatment. Mean (SD) starting visual acuity (VA) of the amblyopic eye was 0.676 (0.337). The mean (SD) VA immediately after treatment improved to 0.368 (0.307). The number of log units' improvement was 0.308. Anisometric amblyopia responded more positively than strabismic amblyopia and mixed amblyopia ($p = 0.021$). Those with moderate amblyopia had a better end visual outcome than those with a severely reduced starting acuity ($p = 0.0004$). Results showed that 49% of patients treated with twice weekly atropine achieved a cure VA, with a further 30% showing a significant improvement.

Conclusions: We found no statistical or clinical significance between the two treatment options (p value = 0.962) in terms of visual outcome. Treatment duration, rate of adverse events and failure-to-attend rates were also comparable. The cost of drug treatment for the average 4 month duration of treatment was significantly cheaper for the twice weekly option. Overall, looking at the successful VA outcomes, low incidence of adverse events, excellent parental compliance and reduced treatment costs, twice weekly atropine proves a favourable option as a first-line treatment for all levels and types of amblyopia compared with daily atropine.

Key words: Amblyopia, Atropine penalisation, Daily atropine, Twice weekly atropine

Introduction

Amblyopia is defined as defective visual acuity (VA) in one or both eyes, which persists after correction of any

refractive error and removal of pathological obstacles. Amblyopia treatment aims to restore VA of the amblyopic eye by means of conventional occlusion or pharmacological penalisation.¹ Pharmacological penalisation involves the instillation of a cycloplegic agent, such as atropine, into the non-amblyopic eye. The action of atropine is to blur near vision even with refractive correction in place, by the prevention of accommodation. The atropine effect degrades slowly, typically wearing off in 7 to 14 days. Atropine penalisation has been shown to be as effective as conventional occlusion for the treatment of amblyopia.^{2,3} It has been reported that the dosage of atropine, whether daily or intermittent, gives the same effective result.^{4,5}

Since 2005, atropine has been offered as a first-line treatment for patients diagnosed with amblyopia at the Royal Victoria Infirmary (RVI), which is part of the Newcastle upon Tyne Hospitals NHS Trust. A recent audit of outcomes showed that 50% of patients (32/65) treated with daily atropine achieved a final VA of 0.250 (logMAR) or better in the previously amblyopic eye and an average improvement of 2.79 (0.014 SD)⁶ log units, which was comparable to published data (2.84 lines).²

The policy for the prescription of atropine at the RVI was altered in 2009. A randomised controlled trial provided evidence to suggest that for moderate levels of amblyopia (0.300–0.600 logMAR) similar levels of VA improvement were obtained whether the atropine was instilled daily or twice weekly.⁵ The aim of this study was to analyse the VA outcomes of patients treated with twice weekly atropine and compare those VA results with the results for patients treated with daily atropine.

Methods

Audit procedure

A retrospective case note review was undertaken for a 1-year period from 1 April 2009 to 31 March 2010. Patients were identified from the orthoptic database and a record of pharmacy prescriptions. The project was registered with the Newcastle upon Tyne NHS Foundation Trusts Research and Development Department.

Eligibility criteria

The departmental eligibility criteria are given below:

- Any type and level of amblyopia present after optimal refractive correction has been worn from diagnosis of reduced vision and a period of refractive adaptation is initiated. Amblyopia therapy is only offered once VA

has stabilised at a sub-normal level for two consecutive visits. Glasses are to be worn full time and time between visits is 6 weeks. This produces a minimum of 12 weeks full-time glasses wear before any amblyopia therapy is offered.

- Three years or older.
- Able to perform a logMAR-based VA test.

Adverse events

Adverse events were pre-defined as follows. A mild adverse event was defined as a reduction in VA of the atropinised eye (0.300 or worse) that did not require further treatment, a mild allergic reaction not requiring further treatment, photophobia or an increase in a manifest deviation. Severe adverse events were pre-defined as a reduction in the VA of the atropinised eye requiring treatment, a severe allergic reaction (swollen lids, red face and rash) requiring treatment and a decompensating heterophoria.

Definition of amblyopia and outcomes

Amblyopia was pre-categorised as:

- moderate: 0.275–0.475;
- severe: 0.500 or worse.

Intraocular difference was not used to define amblyopia.

Acuity outcomes were pre-categorised as follows. A 'cure' outcome was given on reaching a VA of 0.250 or better, 'satisfactory' outcome was defined as VA range of 0.275–0.475 and an 'unsatisfactory' visual outcome was defined as VA 0.500 or worse. Pre-treatment to post-treatment changes in VA were also analysed. These standards are set within the department and are used for all internal audits.

Statistical methods used were the paired *t*-test for comparisons of treatment regimes and severity of amblyopia; ANOVA testing was used for the effect of type of amblyopia. Mean and standard deviation as well as change in VA were also calculated.

Atropine occlusion protocol

Once refractive adaptation had been completed, parents were offered the choice of conventional occlusion or atropine for the treatment of all types and levels of amblyopia. Contraindications to offering atropine are:

- Patients under 3 years of age.
- Inability to perform a logMAR-based test.
- Patients with Down's syndrome and myasthenia gravis.
- Patients with congenital heart problems.
- Patients with angle closure glaucoma.

Atropine 1% was prescribed twice weekly (Wednesdays and Sundays) for an initial period of 6 weeks.

The primary outcome measure was VA assessed using an age-appropriate logMAR test (single Kay's pictures, Crowded Kay's pictures or Keeler Crowded logMAR) immediately following the cessation of atropine therapy. Secondary outcome measures recorded include compliance with treatment and adverse events during treatment. If at any visit VA in the non-amblyopic eye decreased to

worse than 0.300, VA was rechecked with the full optical prescription in place (without allowance for cyclopentolate). If VA improved to 0.300 or better, treatment was continued. If, however, VA was still reduced in the non-amblyopic eye, treatment was discontinued.

Amblyopia therapy continued for 6 months with VA assessments at 6 weeks, 3 months and 6 months. Treatment ceased when either amblyopia was considered to have resolved, parents wished to stop or change treatment, or an adverse event prevented the continuation of treatment. If there was no significant improvement (minimum 0.1 log improvement) in VA after 3 months atropine treatment was supplemented or a change to occlusion considered. Supplements to treatment included the addition of optical penalisation, partial occlusion, conventional occlusion or increased dosage to daily atropine. At the 6-month visit, atropine was discontinued for 1 month prior to treatment re-commencing.

Results

Seventy-one patients aged between 3 and 7 years at the commencement of treatment were identified: 42 males and 29 females. Seventeen patients were identified as having anisometric amblyopia (mean age 5.04 years, SD 1.27 months), 31 strabismic amblyopia (mean age 4.39 years, SD 1.20 months) and 23 with mixed amblyopia (mean age 4.36 years, SD 1.04 months). Thirty-two patients were known to have left amblyopia and 39 right amblyopia. One patient with mixed amblyopia was identified as having a starting vision of 0.225 on Crowded Kay's pictures, but treatment was started due to significant intraocular difference and based on the age-related normal values of this test.⁷ This patient was excluded as they were treated outside the departmental protocol. Therefore 70 patients are included for analysis.

Starting vision ranged from 0.275 (on Crowded Keeler logMAR) to 1.500 (on both Crowded Kay's Pictures and Crowded Keeler logMAR). Twenty-nine patients were classified as having moderate amblyopia (0.275–0.475) and 41 patients had severe amblyopia (0.500 or worse).

All 70 patients were included in the data analysis. Mean (SD) starting VA of the amblyopic eye was 0.676 (0.337). VA immediately after treatment had improved to 0.368 (0.307), showing the mean number of lines improvement in VA to be 0.308 (0.030). Overall cure rate of amblyopia was calculated at 49% (34/70). A further 30% of patients (21/70) had a satisfactory outcome and 21% of patients (15/70) had an unsatisfactory outcome. No patient had a worse final VA in the amblyopic eye compared with their starting vision. A total of 6% (4/70) patients received a supplement to their atropine therapy prescribed at their 3-month follow-up visit. All 4 patients were supplemented with conventional occlusion in a regime of 3 hours per day with twice weekly atropine. Three patients failed to respond to the increase in treatment and VA remained stable for the next two consecutive visits. Treatment was therefore

Table 1. Comparisons of final VA achieved according to type of amblyopia

	No. of patients	Average starting VA (SD)	Average end VA (SD)	Cure rate (%)
Anisometropic amblyopia	17	0.457 (0.212)	0.243 (0.159)	76%
Strabismic amblyopia	31	0.705 (0.358)	0.338 (0.278)	45%
Mixed amblyopia	22	0.804 (0.315)	0.508 (0.382)	31%

discontinued. No pathology was identified to explain the failure to respond to treatment. One patient achieved a cure result, improving from 0.850 to 0.200 on the Crowded Keeler logMAR test over the next 3 months.

Effect of type of amblyopia

The effect of the type of amblyopia on starting and end VA achieved is shown in Table 1. Data analysis showed anisometropic amblyopia responded more positively to treatment compared with strabismic amblyopia and mixed amblyopia (Fig. 1). The type of amblyopia had a significant effect on the end VA achieved ($p = 0.021$). No significant difference in terms of age was identified across the groups.

Effect of starting vision

Starting vision was documented as severe (0.500 or worse) in 41 patients and moderate (0.275–0.475) in the remaining 29. Mean end VA for the group with severe starting acuity was 0.480 (SD 0.367) compared with a

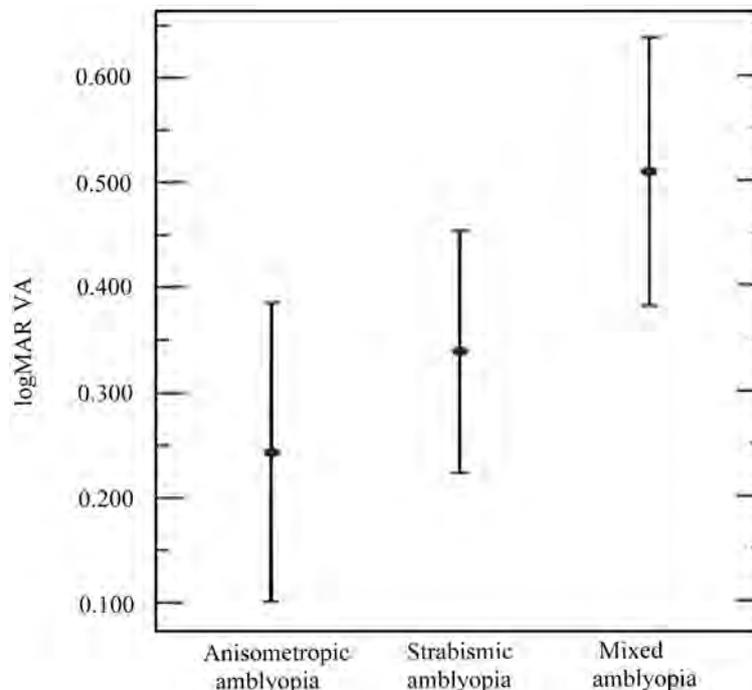
Table 2. Effect of starting acuity on end acuity

	End acuity		
	Cure	Satisfactory	Unsatisfactory
Moderate starting acuity ($n = 29$)	21 (73%)	7 (24%)	0
Severe starting acuity ($n = 41$)	13 (32%)	10 (25%)	13 (32%)

mean end acuity of 0.225 (SD 0.087) for the group with moderate starting acuity. Of those with a severe starting acuity, 32% ($n = 13$) achieved a cure, while 24% ($n = 10$) achieved a satisfactory vision outcome. Of those with a moderate starting acuity 72% ($n = 21$) achieved a cure (Table 2). A paired two-tailed t -test for severe versus moderate starting acuity provided a p -value of 0.0004, showing statistical significance for a superior end visual outcome in those with moderate amblyopia compared with a severe starting acuity.

Effect of atropine on the non-amblyopic eye

Initial starting acuity of the non-amblyopic eye was documented in all 70 patients. Mean (SD) starting acuity without atropine instilled was 0.153 (0.108). Six patients did not complete the treatment due to DNA; VA data are available for all 64 patients who did complete the treatment. VA at the immediate cessation of treatment was documented with atropine instilled in 50 patients and without atropine in 14 patients. Mean (SD; range) VA was 0.166 (0.107; -0.150 to 0.400).

**Fig. 1.** ANOVA plot illustrating the effect of type of amblyopia on end VA achieved. The plot shows the mean end VA for each type of amblyopia and the 95% confidence intervals.

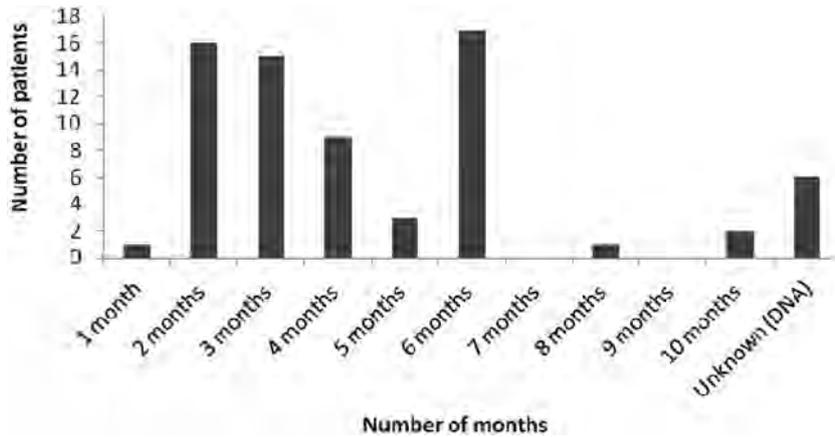


Fig. 2. Range of treatment duration.

Duration of treatment

Treatment duration ranged from 1 to 10 months with a mean of 4 months (Fig. 2). Only 3 patients were in treatment for more than 6 months; as per the protocol they were given a 1-month break. All 3 patients were recorded as having a severe starting level of VA (range 0.625–1.150). All achieved a significant improvement (0.300–0.750) within the treatment window.

For those children who achieved a cure, i.e. VA outcome of 0.250 or better ($n = 35$), treatment duration was shorter: mean 3 months (range 1–6 months).

Adverse events

Six patients (9%) were recorded as suffering from an adverse event directly linked to their atropine treatment. All adverse events were documented as mild and no patient discontinued treatment. Events documented included:

- photophobia ($n = 1$);
- hyperactive behaviour ($n = 1$);
- reduction in vision of the non-amblyopic eye not requiring treatment ($n = 2$);
- increase in manifest deviation ($n = 1$);
- mild allergic reaction not requiring treatment ($n = 1$).

Failure to attend appointments

Six patients (9%) consistently failed to attend appointments following commencement of atropine therapy; 5 of these were recorded as having a severe starting acuity and 1 patient a moderate starting acuity. Five were diagnosed with strabismic amblyopia and 1 with mixed. One patient failed to attend the initial appointment

following treatment prescription and all others had shown no improvement in VA of the amblyopic eye at the visit prior to their failure to attend. For patients who failed to attend, VA outcomes were analysed using the last documented vision result. Fig. 3 shows the details of those lost to follow-up.

Acceptability of treatment

No patients electively chose to change treatment from atropine to conventional occlusion once treatment was under way. All parents reported ease of instillation of atropine and all managed well with an intermittent routine of instillation. From parental reports and examination of pupils on visit dates, compliance was recorded as excellent in all 70 cases.

Comparison of treatment regimes

For daily atropine use, 65 patients were included with a mean starting vision of 0.645 logMAR. A cure rate of 50% was achieved with an additional 34% attaining a satisfactory result. Mean number of lines improvement was 2.79.

For twice weekly use 71 patients were included with a mean starting acuity of 0.670 logMAR. A cure rate of 49% was recorded with a further 30% obtaining a satisfactory result. Mean number of lines improvement was 0.308 (Table 3).

Therefore a paired two-tailed *t*-test was performed on the two data sets and showed no statistical significance between daily atropine and twice weekly atropine (p value = 0.9905) in terms of visual outcome. Treatment duration and rate of adverse events were also comparable.⁶ Equivalent failure-to-attend rates were also documented.⁶

Table 3. Comparison of daily atropine treatment with twice weekly

	Daily atropine ($n = 65$)	Twice weekly atropine ($n = 70$)
Start visual acuity	0.645 (0.288)	0.676 (0.337)
End visual acuity	0.366 (0.277)	0.368 (0.307)
Cure rate	50%	49%
Satisfactory outcome	34%	30%
Lines improvement	0.279 (0.011)	0.308 (0.030)

Discussion

We have reported the results of a retrospective case note review assessing VA outcomes for children treated with twice weekly atropine as a primary treatment for amblyopia. Results showed that 49% of patients treated with twice weekly atropine achieved a cure VA (0.250 or better), with a further 30% showing a significant improvement in their VA and attaining a satisfactory VA

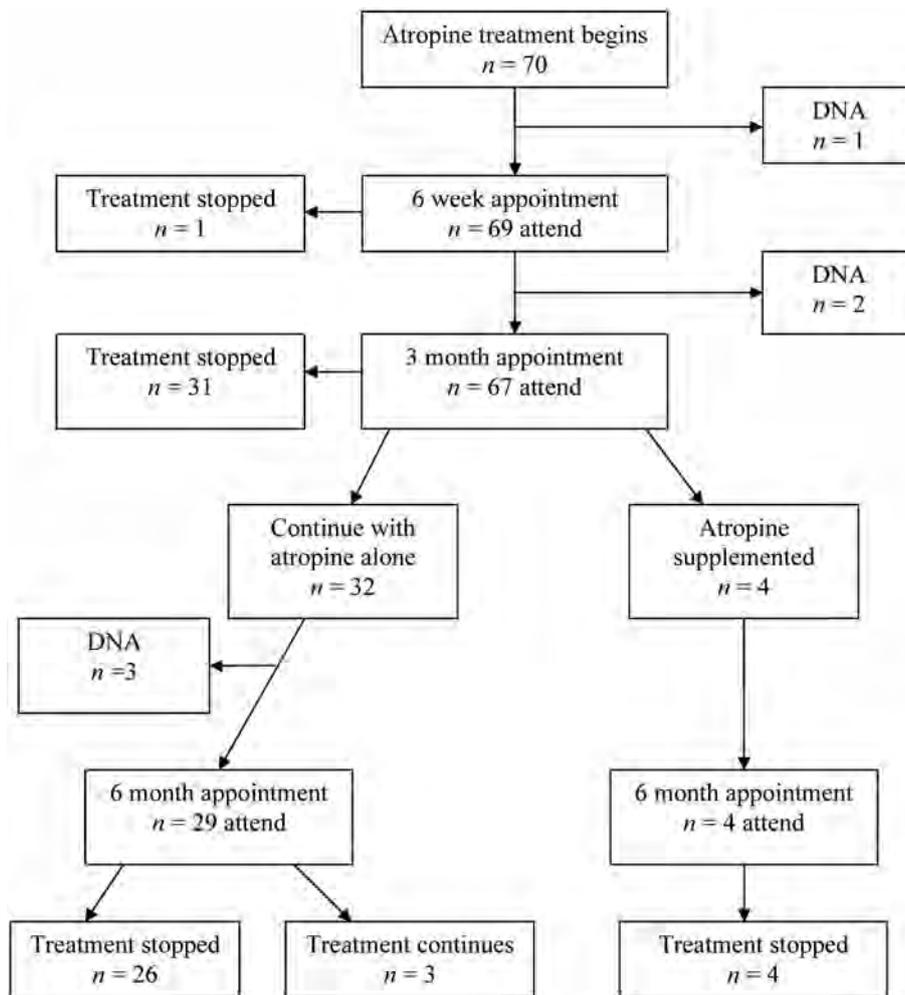


Fig. 3. Flow chart of atropine treatment. DNA, did not attend.

outcome (0.275–0.500). Low incidences of adverse events (9%) were documented. Compliance with treatment measured in terms of attendance at appointments and instillation of atropine via pupil dilation at examination were high. No parent actively chose to discontinue treatment in favour of a different treatment option. Average treatment duration was 4 months (range 1–10 months).

Comparisons have also been made with our previous research of a daily atropine regime, allowing a direct review of both treatments. No statistical or clinical significant difference was found in VA outcomes of the two treatment regimes, daily or twice weekly ($p = 0.99$). Both regimes showed comparable improvement in terms of log units (0.308 for twice weekly, 0.279 for daily) and average treatment duration (4 months). Other published research in this field comparing atropine regimes has also found that intermittent doses of atropine, for example weekend only, yield equivalent vision outcomes to a full-time dose.⁵

The Paediatric Eye Disease Investigator Group (PEDIG) has conducted a randomised control trial of weekend atropine compared with daily atropine. They showed that both treatments gave 2.3 lines improvement

after 4 months, the daily group improving by a further 0.7 lines and the weekend group by 0.8 lines after an unspecified follow-up.⁵ Compared with a previous retrospective study, intermittent atropine (no specified dose) produced an improvement of 1.9 lines in 73 patients and 2.7 lines in 38 patients treated with daily atropine.⁴ Our research adds to the previous known results in this treatment area and provides a comparison between two treatment groups of UK-based participants.

Further research by PEDIG has shown that the augmentation of weekend atropine with optical penalisation (a plano lens placed in front of the non-amblyopic eye) does not enhance the effect of weekend atropine alone.⁸ Atropine has also been proven to be an effective treatment option for older children aged 7–12 years compared with occlusion therapy.⁹ Research has also concluded that the impact of treatment on the family is less negative with atropine compared with occlusion.¹⁰

Prices obtained via our hospital pharmacy show the cost of daily atropine for the average 4-month treatment duration, using minims supplied in a pre-packed box of 20, would be £94.50. This is just the cost of the treatment and does not include any additional cost of the visit incurred from overheads. For twice weekly atropine for

the same treatment duration the cost would be £26.76. It is noteworthy in the current financial climate, with attendant pressures on the NHS to make efficacy savings, that twice weekly atropine is shown in this case set to give the same effective VA outcomes, especially for moderate amblyopia, for just over a quarter of the cost compared with daily atropine.

The limitations of this research are that the study is retrospective and patients were not randomised into treatment groups. However, the results presented are a realistic clinical snapshot of treatment outcomes showing how patients respond to two different treatment regimes. As yet no clinical trial has included a once weekly atropine regime, and given that the cycloplegic effect of atropine lasts 7–14 days this appears to be the next logical stage of research.

Overall, looking at the successful VA outcomes, low incidence of adverse events, excellent parental compliance and reduced treatment costs, twice weekly atropine proves a favourable option as a first-line treatment for all levels and types of amblyopia. As a result of our audit, daily atropine is no longer used for the treatment of amblyopia in our department, and twice weekly atropine is used alongside conventional occlusion.

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