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Is 2% pirenzepine gel effective in slowing the progression of myopia in children aged 7-12 years old?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

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In

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Philadelphia College of Osteopathic Medicine
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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not 2% pirenzepine gel is effective in slowing the progression of myopia in children aged 7-12 years old?

Study Design: Systemic review of three primary randomized controlled trials, which were published in 2008, 2004, and 2005.

Data Sources: Multicenter, randomized double masked, placebo controlled, randomized controlled trials (RCT) were found using PubMed, COCHRANE, and OVID databases.

Outcome measured: The outcome, slowing of myopia progression, was measured similarly in all three trials. Progression of myopia was measured via changes in refractory status and spherical equivalence specifically defined as >0.75D after 12 months of treatment.

Results: In all, the results found that children receiving 2% pirenzepine gel as opposed to placebo did have a decrease in their progression of myopia. In the study Tan et al, it was reported that myopia progression in the gel receiving group was averaged to be 0.47D while the placebo group progressed 0.84D over the one year trial. The study done by Siatkowski et al discovered that after a 2 year trial the group receiving treatment had a slower progression of myopia (0.58D) than the placebo group (0.99D). Overall, pirenzepine was effective in slowing the progression of myopia.

Conclusion: The results of the three RCT revealed that the use of 2% pirenzepine gel was safe and slowed the progression of myopia when compared to the placebo group.

Key words: myopia, pirenzepine, progression

Introduction

Myopia, also known as nearsightedness, is one of the most common ocular disorders. In this condition the eye undertakes a myopic crescent anatomy therefore causing the eye to enlarge and lengthen in the posterior segment[1]. The change in normal optic anatomy causes light rays to be focused in front of the retina instead of the space on the retina. Axial myopia is due to the cornea or lens curvature being too strong or the eye too long[2]. This causes images closer to be viewed clearly and those further away to appear blurry. The exact cause of myopia is unknown and there are no means to preventing it. Treatment options are available which include visual training, bifocals, lenses, surgery, and pharmaceuticals[3].

Myopia is among the leading causes of blindness and visual impairment in the world. It has a high prevalence all over the world and has been found to affect women twice as much as men. This condition is most often diagnosed in children between 8-12 years old and can progress throughout a persons' lifetime. It is estimated that worldwide there are 80 million myopic children[4]. In the US, approximately 30% of the population has a form of myopia[2]. The National Eye Institute conducted a study in 2008 which found that the prevalence of myopia had increased 66% in the US alone between 1971- 1972 and 1999-2004[5]. There is not an exact estimate available for world costs of myopia and its treatments. In the US the treatment of myopia is predicted to cost an estimated $250 million per year[2]. Although the exact estimate for healthcare visits per year is also unknown, millions of Americans receive some form of treatment for myopia. It is estimated that 36 million Americans wear contact lens, 150 million Americans use corrective eyewear and in 2010, 800,000 refractive surgical procedures were performed[8].

Myopia is a refractory error with unknown etiology but hereditary and visual stressors are two risk factors that contribute to its development. Most people that suffer from myopia can be classified into two groups. Patient's whose spherical equivalence (SE) is less than -6.0D would

fall under the category of physiological or "school" myopia. This is the most prevalent form and is considered a normal biological variation. In patients that have a SE greater than -6.0D are categorized as high or pathological myopia. It is believed that this is caused when axial lengths fail to stabilize during normal young adulthood. Pathological myopia is a progressive, degenerative form of myopia that has a high incidence of retinal detachment and glaucoma [1].

The exact etiology of myopia is unknown but there are various known risk factors. Physiological myopia is believed to be a response to stress on the eye. There is evidence that increased time spent reading from teens to mid- 20s is related to school myopia[1]. Other factors, such as race and ethnicity can contribute to nearsightedness. For instance, Asians and people of Jewish decent have the highest prevalence while blacks have the lowest[1].

Myopia can be corrected with glasses, contact lenses, bifocals, or surgery. Although these treatments help correct myopia, they do not treat the underlying physiological condition. Glasses and contact lenses are the easiest and fastest technique in correcting nearsightedness. Contact lenses work by acting as the first refractive surface before light rays enter the eyes while glasses or bifocals have a concave lens that allow for light to focus over a longer distance. This allows for light to focus on the retina[3]. Refractive surgery usually involves a laser that permanently alters the shape of the cornea. One type of surgery, known as PRK, removes a layer of corneal tissue allowing for the cornea to flatten and light to focus on the retina. LASIK procedure creates a thin flap on the cornea and removes corneal tissue and then returns the flap. Also, orthokeratology is another treatment option for patients with myopia. This is a non-surgical procedure where rigid or permeable contact lenses are worn at night to reshape the cornea. Although this is a temporary treatment it can help correct mild to moderate myopia[3]. There is no known preventative treatment for myopia. It is believed that visual training can help "control"

myopia. These techniques may include muscle relaxation, eye massage, or biofeedback. There is no evidence that these techniques help prevent or treat nearsightedness[3].

The goal of using pirenzepine gel is to prevent the progression of myopia. By preventing the progression of myopia, it decreases the chance for the patient to develop macular degeneration, retinal detachment, and glaucoma[1]. Several studies have showed that the use of muscarinic antagonists, such as atropine, which bind to M3 and M1 receptors, can slow the progression of myopia in children. Pirenzepine is a selective M1 muscarinic receptor antagonist that is believed to have fewer side effects than atropine. In animal trials, pirenzepine was able to reduce deprivation-induced myopia and axial elongation. This drug is normally used to treat dyspepsia and pediatric endocrine disorders and has a great safety profile[6].

Objective

The objective of this selective evidence based medicine (EBM) review is to determine whether or not 2% pirenzepine gel is effective in slowing the progression of myopia in children aged 7-12 years old.

Methods

The three studies that are included in this EBM review are multicenter, double masked, placebo controlled, randomized controlled trials (RCT). The criteria used for these studies were based off of population and severity of nearsightedness. Patients were aged 7-12 with myopia defined as a spherical equivalent (SE) of -0.75 to -4.00D and astigmatism of $\leq$1.00D in each eye[4, 6, 7]. The treatment group received the intervention of 2% ophthalmic gel while the experimental group received a placebo ophthalmic gel. These two groups were compared to discover if an overall efficacy in slowing the progression of myopia was present and if use of the gel was tolerable in children. Two of the three trials conducted the study for 1 year while the remaining study was conducted for two years.

Key words used in the searches were “pirenzepine”, “myopia”, and “progression.” The databases used were COCHRANE, OVID, and PubMed. All articles were published in English in peer reviewed journals. I researched the articles and each article was selected based on relevance to my chosen topic and that each study included patient oriented outcomes (POEM). My inclusion criteria encompassed randomized controlled trials published after 1996 with a population aged 7-12 years. The exclusion criteria included children below age seven and greater than age 12 or had already tried pirenzepine or surgical treatment. Summary of statistics used were RRR, AAR, NNT, and p-values.

Table 1: Demographics & Characteristics of included studies

Study	Type	#Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Intervention
Siatkowski (2008)[4]	Double Blind RCT	84	8-12 y.o	Patients were aged 8-12 and had best corrected visual acuity of >20/25 in each eye	Patients with current use of contact lenses or bifocals, history of ocular trauma, disease or surgery, hypersensitivity to topical anesthetics, mydriatics	1	2% Pirenzepine ophthalmic gel twice daily for two years; Placebo ophthalmic gel twice daily for two years
Siatkowski (2004)[7]	Double Blind RCT	174	8-12 y.o	Patients were aged 8-12 and had best corrected visual acuity of >20/25 in each eye	Patients with current use of contact lenses or bifocals, history of ocular trauma, disease or surgery, hypersensitivity to topical anesthetics, mydriatics	29	2% Pirenzepine ophthalmic gel twice daily for 1 year; placebo ophthalmic gel twice a day for 1 year
Tan (2005)[6]	Double Blind RCT	353	6-12 y.o	Patients were healthy, aged 6-12 and had best corrected visual acuity of >20/25 in each eye	Patients with current use of contact lenses or bifocals, history of ocular trauma, disease or surgery, previous use of atropine	23	2% Pirenzepine ophthalmic gel twice daily for 1 year; placebo ophthalmic gel twice a day for 1 year

Outcomes

The outcomes measured the progression of myopia. This was primarily measured by changes in refractory status and spherical equivalent (SE). Refractory error is an error in the ability of the eye to focus light and is a frequent reason for reduced visual activity. When focusing does not work accurately, it results in blurred vision. Refractive error is related to the ocular axial length therefore if there is in increase in axial length, there will be an increase in the refractive error which causes a worsening of myopia. The SE is the refractory error but in measurement form and is what optical prescriptions appear as. This measurement in diopters is the unit of measurement of the optical power of lens. The higher the diopters or SE is, indicates the severity of myopia.

Results

All three articles compared the use of pirenzepine with the use of a placebo to retard the progression of myopia in patients aged 7-12. All three studies were double masked, placebo-controlled, RCTs. The identity of treatment was masked from the children, parents, and investigators. The primary outcome measure for all three studies was myopia progression via spherical equivalence. All patients were treated as outpatients.

Tan et al studied a total of 353 participants, aged 6 to 12 years with myopia defined as a spherical equivalent of -0.75 to -4.00D and astigmatism of $\leq$1.00D in each eye. Patients excluded from the study were ones with a spherical equivalent of >1.00 D, strabismus, current use of contact lenses or bifocals and history of ocular surgery, trauma, chronic ocular disease, or previous use of atropine for retarding myopia progression. Each patient underwent the study for 1 year as out patients and was randomly given either 2% pirenzepine gel or placebo gel packaged in identical tubing. The medication was to be administered twice daily as a 6mm stripe in the cul-de-sac of the lower eyelid. Compliance monitoring started 6 months after the study had started

with an electronic compliance monitoring device (ECMD). Patients had their SE measured at 3, 6, 9, and 12 months under cycloplegic refraction. At entry the mean SE was -2.4 + 0.9D. A reduction in the progression of myopia over one year was observed where the mean increase of myopia was 0.47D in the gel group and 0.84D increase in the placebo group ($p < 0.001$, CI 95%, placebo -3.29$\pm$ 1.02, gel -2.82$\pm$1.02) . The NNT for the one year study indicated that 4 patients would need to be treated with 2% pirenzepine gel in order to have one fewer with progression of myopia when compared to placebo (Table 2)[6].

During the one year study, 11% of pirenzepine treated subjects discontinued the study due to adverse events. There were 15 serious adverse events reported in 12 subjects, none of which were ophthalmic in nature and all patients recovered. All side effects were mild to moderate in nature and the most common of which was follicles/papillae (Table 3). The NNH for this study was 9 meaning that for every 9 subjects treated with pirenzepine one additional patient would experience any of the possible side effects (Table 4)[6].

Table 2: Analysis of NNT among participants receiving 2% pirenzepine

Relative Risk Reduction (RRI)	Absolute risk Reduction (ARI)	Number needed to treat (NNT)
-0.49	-0.28	-4

Table 3: Adverse side effects in participants receiving 2% pirenzepine gel vs. placebo[6]

Side Effect	% pirenzepine treated subjects	% placebo treated subjects
Follicles/papillae	59	14
Medication residue	52	49
Abnormality of accommodation	44	3
Cough	23	23
Abdominal Pain	9	1

Table 4: Analysis of all adverse events among participants receiving pirenzepine

Relative Risk Increase (RRI)	Absolute risk Increase (ARI)	Number needed to harm (NNH)
.11	.11	9

The two studies published by Siatkowski et al both had a population of healthy children, aged 8 to 12 years old, with a SE of -0.75 to -4.00D and astigmatism of 1.00D or less. Each study had the same inclusion and exclusion criteria (see Table 1). The study published in 2004 was conducted for 1 year and had a population size of 174 children. The subjects were randomly given either 2% pirenzepine gel or placebo gel. Patients were instructed to use their "medication" daily and keep their eyes closed 1 minute after use. Each patient was properly instructed with demonstration from clinical staff. At 3, 6, 9, and 12 months the patients received eye exams and the primary clinical outcome was measured. At study entry the mean SE refraction was -2.098 $\pm$ 0.903 for the pirenzepine group and -1.933 $\pm$ 0.825 for the placebo group. At 12 months the mean increase in myopia in the pirenzepine group was 0.26D vs. 0.53D in the placebo group ($p<0.001$, CI 95%, pirenzepine -2.42$\pm$ 0.99, placebo -2.41 $\pm$ 1.04). The NNT for the one year study indicated that 5 patients would need to be treated with 2% pirenzepine gel in order to have one fewer with progression of myopia when compared to placebo (Table 5)[7].

Table 5: Analysis of NNT among participants receiving pirenzepine in 1 and 2 year study

Study	**Relative Risk Reduction (RRR)**	**Absolute risk Reduction (ARR)**	**Number needed to treat (NNT)**
Siatkowski 2004[7]	-0.645	-0.20	-5
Siatkowski 2008[4]	-0.46	-0.31	-4

The two year study published by Siatkowski et all (2008) had 84 participants all of whom satisfactorily underwent the previous one year study. At the end of the two year study, the pirenzepine group had a mean increase in myopia of 0.58D and 0.99D for the placebo group ($p=0.008$, pirenzepine -2.84 $\pm$ 1.04, placebo -2.82$\pm$ 1.13) . The NNT for the one year study

indicated that 4 patients would need to be treated with 2% pirenzepine gel in order to have one fewer with progression of myopia when compared to placebo (Table 5)[4].

In the one year study, 13 patients (11%) of the pirenzepine group discontinued the study due to adverse side effects while none of the placebo subjects had. The three most frequent systemic events were headache and cold and flu syndrome. The most common ocular events were mydriasis, erythema of the eyelids, and ocular itching (Table 6). The NNH for this study was 9 meaning that for every 9 subjects treated with pirenzepine one additional patient would experience any possible side effect (Table 7)[7].

Table 6: Adverse side effects in participants receiving 2% pirenzepine gel vs. placebo in 1 year study[7].

Side Effect	% pirenzepine treated subjects	% placebo treated subjects	*P* value
Headache	29	28	>0.99
Cold	20	40	.006
Flu syndrome	16	18	.83
Mydriasis	9	2	.10
Erythema, eyelids	7	4	.50

The two year study only had one patient drop out due to adverse side effects. This study had the same ocular and systemic side effects as the one year study. The NNH for this study was 84 meaning that for every 84 subjects treated with pirenzepine one additional patient would experience any one of the same side effects as the previous 1 year study (Table 7)[4].

Table 7: Analysis of adverse events among participants receiving pirenzepine

Study	Relative Risk Increase (RRI)	Absolute risk Increase (ARI)	Number needed to harm (NNH)
Siatkowski 2004[7]	.11	.11	9
Siatkowski 2008[4]	0.012	0.012	84

Discussion

The three RCTs reviewed for this paper demonstrated the effectiveness of 2% pirenzepine gel in comparison to placebo in retarding the progression of myopia in children. All three studies mainly studied children from Asia but other studies have shown similar effects in children in the United States[9]. Also, these RCT only looked at safety in children but other studies have displayed tolerability and safety to the drug in adults[4].

Pirenzepine hydrochloride is a "selective" muscarinic receptor antagonist that specifically works on the M_1 receptor. It has been used for years in Europe and Asia. It is normally used to treat peptic ulcers and pediatric endocrine disorders. For ocular therapy, due to it being a selective muscarinic antagonist, it is less active on the pupil and ciliary in the body. This prevents dilation of the pupil and decreases the loss of ability to focus, which is commonly seen with atropine use. It is commonly used in children >12 years and adults. It is well tolerated by most patients with low incidence of anti-muscarinic effects. Anti-muscarinic side effects that may present are dry mouth, blurred vision, drowsiness, nausea, loss of appetites, decreased sexual desire. There are no black box warnings against the drug but it is not approved by the FDA in the USA[10].

Limitations were noted in the three RCT. Potential limitations found in the three studies included lack of formal accommodation testing in the second year study and a slight difference in baseline myopia between the pirenzepine and placebo group. Although the baseline difference was not considered statistically significant it can still be seen as a potential limitation. Additionally, there was no difference in family history between the placebo and pirenzepine participants and all patients were of Asia ethnicity. Diversity in participants between each group could allow for more information to be obtained about myopia. Also, all patients in the study had

a SE that categorized them as having physiological myopia. The effects of the medication on children with pathological myopia was not studied..

Conclusion

2% pirenzepine gel is an effective treatment for slowing the progression of myopia in children. All three RCTs in this review were able to provide significant evidence that treatment with this drug could reduce progression of myopia. Drug safety was also significantly proven as each study only had mild to moderate adverse effects in a low percentage of patients.

There are only a few flaws in these studies. The most significant flaw was providing proof of compliance during the study. Tan et al had started testing for compliance half way through the studies with EMCD. By knowing compliance rates in both pirenzepine and placebo groups can alter interpretations of statistical findings.

Myopia is a very common ocular disease and has been steadily increasing throughout populations in the world. It is important to conduct future studies pertaining to slowing the progression of myopia due to its increasing prevalence. In the future, studies of longer duration should be done to discover optimal length of treatment. Also, future studies should include more convenient and practical methods of drug administration, for example optic drops or systemic pills. Future studies should also be done to analyze the effect of the medication on patients with pathologic, progressive myopia. Future studies should also be done to analyze the effect of the medication on patients with pathologic, progressive myopia. Finding a drug that is safe and successful in slowing down the progression of myopia or even stopping it is an integral part to finding a cure for myopia.

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