Study of the Efficacy of Homoeopathic Ruta graveolens on Progression of Simple Myopia

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ABSTRACT

Background and aim: Simple myopia is a refractive error that begins between 5 to 13 years of age, progresses till 25 years. Recent increase in its incidence and progression was mainly attributed to excess near work. Homoeopathy mentions Ruta graveolens for myopia with its action on accommodation and sclera, so it was considered for this study with an aim to assess its efficacy on controlling myopia.

Design: Parallel-group, randomized, double-masked, placebo-controlled study.

Methods: 125 subjects aged 7 to 25 years with spherical refraction -1.0 to -10.0 diopters (D) and astigmatism d" -2.0 D were enrolled. Either Ruta 3C or placebo in 3: 2 allocation ratio was given with a dose of 4 globules BD orally for 21 days thereafter a gap of 7 days for 2 years. Refraction in diopters was checked by subjective method and axial length in mm by A Scan biometer after every 8 months.

Results: 108 subjects who have completed 2 years study with 66 subjects in Ruta group and 42 in placebo were analyzed. Mean change in refraction and axial length in placebo group was -1.12 ± 0.07 D and 0.71 ± 0.07 mm, while in Ruta -0.63 ± 0.06 D and 0.39 ± 0.04 mm respectively. The difference in refraction and axial length between the two groups of 0.49 D and -0.32 mm respectively was found statistically significant. ($P < 0.001$)

Conclusion: Ruta 3C was effective in controlling ocular refraction and axial length.

Keywords: Homoeopathy, Myopia, Randomized controlled trial, Ruta graveolens

INTRODUCTION

Myopia (short sight) is a refractive error where an individual affected has dimness of vision for distant objects. It is defined as that dioptric condition of the eye in which with accommodation at rest; incident parallel rays of light come to a focus anterior to light sensitive layer of the retina. [1] Simple (childhood) myopia is a common variety of axial myopia which commences between 5 to 13 years of age, progresses during the period of body growth and after 25 years no major progression occurs. [2]

Heredity does play an important role in etiology of myopia, however worldwide increased in its prevalence and progression during last few decades was attributed to environmental factors especially excessive accommodation during near work associated with competitive education and urbanization. Different human studies have shown deficient accommodation in myopes than emmetropes. This weakness of accommodation cause hyperopic retinal defocus during excessive near work leading to myopia.[3] So researcher claims that *myopia occurs due to combined effect of genetic predisposition and excess near work that act as a triggering factor.*

Myopia prevalence is as high as 70 to 90% among East Asian countries such as in Singapore, Hong Kong, Taiwan and Japan, while 30 to 40% in Europe, United

States and 10 to 20% in Africa. [4] In India it varies from 6.9 to 14% in various surveys. Myopic individuals face lot of ocular, financial, educational and occupational problems in future. Lot of research is going on world over to control myopia and different measures used were vision therapy techniques, use of optical devices and local use of modern medicines. Out of these, *Atropine sulfate* 1% eye drops and Pirenzepine 2% ophthalmic gel were found effective in controlling myopia. However they are not yet approved as standard treatment due to their local or systemic side effects, ethical issues associated with its long term use and rebound effect after discontinuation of treatment. [3] Laser refractive surgery only corrects the existing myopia, so it is not recommended till myopia gets stabilise. So there is a great need to have a medical treatment that will be effective, safe, economical and easy to use to control myopia.

In Homoeopathic literature different medicines are mentioned for myopia. However they are used in different varieties of myopia such as simple myopia, pathological myopia, pseudo myopia, induced myopia etc. Out of these simple myopia associated with near work is a concerned, *Ruta graveolens* (Ruta) seems to have more symptom-similarity to myopia as compared to other medicines. [5] This can be appreciated from following points :

A) References from homoeopathic literature: Ruta is indicated in ailments from overstraining eyes, from reading too much, especially fine work at night. [6] Ruta has affinity for sclerotic portion of eye. [7] Moffat [8] and Norton [9] have stated use of Ruta in weakness of ciliary muscles." Allen T.F. [10] has specifically mentioned that "Ruta is valuable in weakness of accommodation especially in nearsighted people." Book of Hahnemann's Materia Medica Pura [11] & T. F. Allen's "The Encyclopedia of Pure Material Medica" [12] have mentioned signs & symptoms of myopia in provers during Ruta drug proving.

B) Gradation of myopia medicine: A repertorisation was done with the help of homoeopathic software to grade myopia medicines. Rubrics for repertorisation were medicines having affinity for eyes and sclera, medicines under myopia / short sight, signs and symptoms of myopia. Result has shown that Ruta covered more rubrics & counted higher number of marks in repertorial totality.

C) References from historical literature: Ancient Egyptians and early Greeks believed that Ruta taken orally could improve their eye sight and was popular among artists, craftsmen and writers who needed good vision to perform their near work. It is still eaten by Italian in their salads and was supposed to make the sight sharp and clear particularly when the vision had become dim through over exertion of the eyes. [13]

D) References from botanical literature: Rutin and Quercetin are the flavonoids in the drug Ruta. [14] Numerous publications have mentioned antioxidant properties of flavonoids. There is a correlation of higher grade of myopia and an elevated level of oxidative process. So flavonoids in Ruta have got a beneficial effect on myopia. Thus Ruta can be considered as a nutritive remedy.

E) Preliminary clinical study: a study of *Physostigma* venenosum on myopia was done by Dr. Basu. [15] A retrospective clinical study about the effect of Ruta and Physostigma on myopia was done in Sathye eye research institute for alternative medicines, Pune. The study has shown beneficial effects of Ruta on myopia as compared to *Physostigma*. A search on internet revealed that there was no published clinical study of Ruta on myopia.

So by taking into consideration the above facts, a controlled clinical study of Ruta on myopia was planned.

Objectives:

- To determine the effect of Ruta and placebo on Spherical Equivalent of Refraction (SER) and ocular Axial Length (AL).
- To compare the effects on SER and AL between two groups.
- To study the grade of improvement based on refraction in two treatment groups.
- To study the baseline characteristics of those benefitted in Ruta-treated group.

MATERIAL AND METHODS

Study Design:

A parallel group, randomized, double-masked (blind), placebo-controlled clinical study was done in OPD patients of Sathye Eye Research Institute for Alternative Medicines, Pune, Maharashtra, India, during November 2005 to June 2010. The study protocol was in accordance with the Helsinki's declaration on

human experimentation. [16] The institutional ethical and expert committee approved the protocol. The study was registered retrospectively in Clinical Trial Registry-India, [17] number being CTRI/2014/10/005109. A standardized case record form was prepared for case taking and help of consultant ophthalmologist was taken during this study.

Participants:

Subjects were collected from OPD of institute during November 2005 to November 2007. Subjects included were diagnosed cases of simple progressive myopia between the age group 7 to 25 years irrespective of sex, race, diet and socioeconomic status. Degree of myopia between -1.0 to -10.0 D of spherical refraction, astigmatism of -2.0 D or less and visual acuity up to 6 / 6. Area of recruitment was from Pune city.

Subjects excluded were those with simple myopic astigmatism, high myopia with retinal degeneration, squint, amblyopia and other ocular disease, history of refractive surgery, contact lens users and those undergoing treatment for general diseases.

Intervention:

Homoeopathic Ruta graveolens 3 Centesimal (C) potency was procured from a licensed homoeopathic pharmacy in sufficient amount, so that same batch can be used throughout the study. Globules moistened with dispensing alcohol were used as a placebo. Globules of size 30 and 2 dram glass bottles were used for dispensing. Subjects were treated either with Ruta or placebo with a dose of 4 globules twice a day for 21 days thereafter a gap of 7 days for the duration of 2 years.

Sample size:

Sample size estimation was based on assumption that myopia in placebo group would progress by a mean of -0.6 D per year [18] with standard deviation of 0.5 D. We assumed an arbitrary effect difference of 50% between the Ruta verses placebo group on refraction (SER), allowing 15% attrition. Minimum sample size of 145 was estimated with 87 subjects in Ruta treated group and 58 in placebo group with an allocation ratio of 3: 2 for a power of 90% with a two-sided test of 5% significance. [19] Total 150 subjects were considered for this study with 90 subjects in Ruta and 60 in placebo treated group.

Random assignment:

Computer generated Random Number Table (RNT) was prepared for 150 numbers with a place marker across. [20] All 2 dram bottles were coded as per RNT. Initial 90 coded bottles with a place marker p1 to p90 were filled with Ruta medicated globules while remaining 60 coded bottles were filled with placebo. So there was an unequal assignment with allocation ratio of 3: 2 between Ruta and placebo-treated group respectively. 150 pre-coded identical bottles were arranged in ascending order of their code numbers from 1 to 150 and kept at the place of research.

Details of Procedure:

Subjects fulfilling selection criteria were informed verbally and on written pamphlet about the details of myopia and its study procedure. Their general fitness was assessed with physical examination and laboratory investigations. Physically fit subjects were called with an appointment and a written informed consent was obtained. In case of minor, consent of their parents and a written assent of subject were obtained. Detail history was recorded on a case paper. Before starting eye examination reliability of all instruments was assessed. During eye examination, an uncorrected distant vision was checked on Snellen's chart in each eye separately. Objective (cycloplegic) refraction was carried out with *Cyclopentolate hydrochloride* 1% eye drop with the help of a retinoscope. [21]

On next visit, subjective refraction was carried out by taking into account readings of objective refraction till visual acuity of 6 / 6 was achieved. Duochrome test with red green strips on vision testing drum was carried out to finalize subjective refraction. [22] Axial length of eyeball was measured with "A Scan biometer," an ultrasonography instrument (Model 3000 A, DGH Technology Inc. USA). Before measurement, local anesthetic *Proparacain hydrochloride* 0.5% eye drops were instilled twice approximately 30 seconds apart. Total 8 consecutive readings were taken, so that at least 5 were within range of 0.20 mm. which is an acceptable limit.[23] Out of these a reading with 3 display spikes of higher amplitude and almost equal height was finalized.

Outcome measures:

Primary outcome efficacy measure was a change in Spherical Equivalent of Refraction from baseline in

diopters assessed by subjective refraction after every 4 months. It is defined as spherical power plus half of cylindrical power. Secondary outcome measure was change in axial length from baseline measured in mm by A Scan biometer after 8 months.

To ensure the *validity of measurement*, every time eye examination was carried out with the same instrument, by the same examiner, at the same place and preferably during the similar timings of the day.

Instructions for patients:

Subjects were advised to chew the medicated globules and not to take any food or drink for half an hour before or after it. No alteration in diet and regimen was suggested. *To ensure compliance* with the treatment regimen a 'pill intake register paper' containing calendar tables was prepared. Parents were advised to tick morning and evening row of table after giving medicine and to make a signature on it at the end of day. All subjects were advised to use corrected glasses.

Procedure during follow up:

Subjects were told to inform about any general or ocular complaints during their follow up visits. If subjects suffered from any illness, they were either given homoeopathic medicine or allowed to take medication from their family doctor. During this period study medicine was withheld. If a change of $\geq$ 1.0 D of refraction occurs, corrected glasses were prescribed. Subjects who fail to keep follow up for more than 3 consecutive months or those who wish to go for contact lenses were withdrawn from study. After 2 years of study code numbers were revealed and data entry on computer was finalized.

Method of Masking (Blinding):

Statistician prepared a RNT and handed it over to a third party person who filled either Ruta or placebo globules in 2 dram bottles as per RNT. On every visit examiner recorded eye examination findings on a new follow up paper labelled with a code number of subject, so he has no idea about previous examination findings as well as was unaware about the group a particular subject belongs to. Subjects were given pre-coded identical 2 dram bottles containing Ruta or placebo globules having a similar appearance (size, shape, color) and odor. So subjects or their guardians were unaware about the group allocated.

Method of statistical analysis:

Subjects who have completed study period of 2 years were analyzed. Average of both eyes was used to evaluate the magnitude of change in SER and AL from baseline to follow up visits. Student's *t* test was used to analyzed the results. Probability value (*P*) of < 0.05 was considered statistically significant. SPSS software version 10 was used to analyse the results.

RESULTS

Flow of participants:

Out of 132 myopic subjects assessed for eligibility 7 were excluded. One hundred and twenty five eligible subjects were randomly assigned to 78 in Ruta-treated group, while 47 in placebo-treated group. One hundred and eight subjects (86.4%) completed study period of 2 years. Out of 17 subjects who were either withdrawn or lost to follow up, 12 were from Ruta group and 5 were from placebo (figure 1).

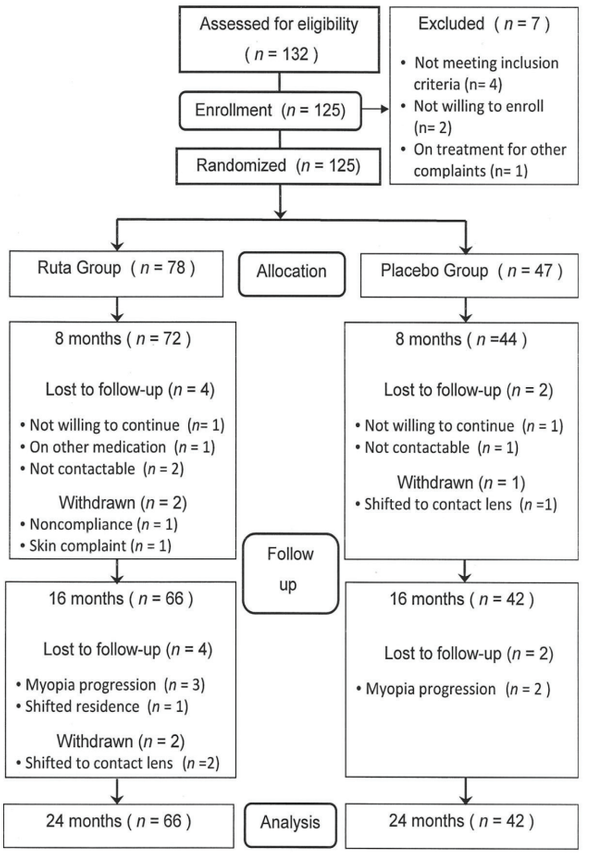

Figure 1 : Flow of participants and the reasons of their dropout in the study.

Baseline balance:

Homogeneity or balance between two groups in retained subjects was assessed in different baseline characteristics such as age, gender, near work hours, parental myopia, SER and AL. There was no statistically significant difference between two groups (table 1). Similarly baseline characteristics of subjects in whole group were similar to those retained after attrition in their respective group (table 2, 3).

Table 1: Balance between two groups by their baseline characteristics in retained subjects.

Baseline Characteristics	Ruta group(*n* = 66)	Placebo group(*n* = 42)	*P*Value
Age, mean ± SD (Yrs.)	12.97 ± 3.50	14.14 ± 3.17	0.07
Gender males, n (%)	34 (51)	23 (55)	0.74
Near work, mean ± SD (Hrs.)	4.16 ± 1.51	3.71 ± 1.21	0.09
Parental myopia, n (%)	27 (41)	23 (55)	0.16
SER, mean ± SD (D)	-3.35 ± 1.54	-3.55 ± 2.21	0.61
AL, mean ± SD (mm)	24.30 ± 1.00	24.07 ± 0.98	0.25

Abbreviations : SER – Spherical Equivalent of Refraction, D – Diopters, AL – Axial Length.

Table 2 : Baseline characteristics in total, dropout and retained subjects and balance between total and retained subjects in Ruta-treated group.

Baseline Characteristics	**Total Ruta (n = 78)**	**Dropout Ruta (n = 12)**	**Retained Ruta (n = 66)**	**P Value (Total & Retained)**
Age, mean ± SD (Yrs.)	13.14 ± 3.49	14.08 ± 3.40	12.97 ± 3.50	0.77
Gender males, n (%)	40 (51)	6 (50)	34 (51)	0.98
Near work, mean ± SD (Hrs.)	4.09 ± 1.48	3.71 ± 1.27	4.16 ± 1.51	0.78
Parental myopia, n (%)	35 (45)	8 (67)	27 (41)	0.63
SER, mean ± SD (D)	-3.39 ± 1.55	-3.59 ± 1.65	-3.35 ± 1.54	0.88
AL, mean ± SD (mm)	24.33 ± 0.99	24.49 ± 0.97	24.3 ± 1.00	0.86

Table 3 : Baseline characteristics in total, dropout and retained subjects and balance between total and retained subjects in Placebo-treated group.

Baseline **Characteristics**	Total **Placebo** (*n* = 47)	Dropout **Placebo** (*n* = 5)	Retained **Placebo** (*n* = 42)	*P* Value (Total & Retained)
Age, mean ± SD (Yrs.)	14.3 ± 3.38	15.6 ± 5.13	14.14 ± 3.17	0.82
Gender males, n (%)	25 (53)	2 (40)	23 (55)	0.88
Near work, mean ± SD (Hrs.)	3.7 ± 1.24	3.6 ± 1.67	3.71 ± 1.21	0.96
Parental myopia, n (%)	24 (51)	1 (20)	23 (55)	0.73
SER, mean ± SD (D)	-3.56 ± 2.11	-3.63 ± 1.16	-3.55 ± 2.26	0.99
AL, mean ± SD (mm)	24.06 ± 0.96	23.97 ± 0.87	24.07 ± 0.98	0.96

Results on refraction and axial length in two groups:

After 8 months, mean change in SER from baseline in Ruta-treated group was -0.20 ± 0.04 D, while in placebo group -0.44 ± 0.04 D. The difference in means between two groups of 0.24 D was statistically significant (95% CI: 0.12 to 0.36; *P* = < 0.001). Mean change in AL was 0.16 ± 0.04 mm in Ruta group and 0.25 ± 0.05 mm in placebo group respectively and difference in their means of -0.09 mm was not statistically significant (95% CI : -0.21 to 0.03; *P* = 0.145).

After 16 months, mean change in SER from baseline in Ruta and placebo-treated group were -0.48 ± 0.05 D and -0.73 ± 0.06 D respectively. The difference in their means of 0.25 D was statistically significant (95% CI: 0.09 to 0.41; *P* = 0.003). Similarly mean change in AL was 0.26 ± 0.04 mm in Ruta and 0.51 ± 0.08 mm in placebo group. The difference in their means of -0.26 mm was statistically significant (95% CI : -0.42 to -0.10; *P* = 0.002).

After 24 months, mean change in SER and AL from baseline in placebo-treated group was -1.12 ± 0.07 D and 0.71 ± 0.07 mm and in Ruta group it was only -0.63 ± 0.06 D and 0.39 ± 0.04 mm respectively. The difference in their means between two groups in SER of 0.49 D was found statistically significant (95% CI: 0.31 to 0.67; *P* = < 0.001) and in AL -0.32 mm was also statistically significant (95% CI: -0.47 to 0.16; P = < 0.001). Mean SER and AL values at baseline and different visits were plotted in figure 2 and 3 respectively.

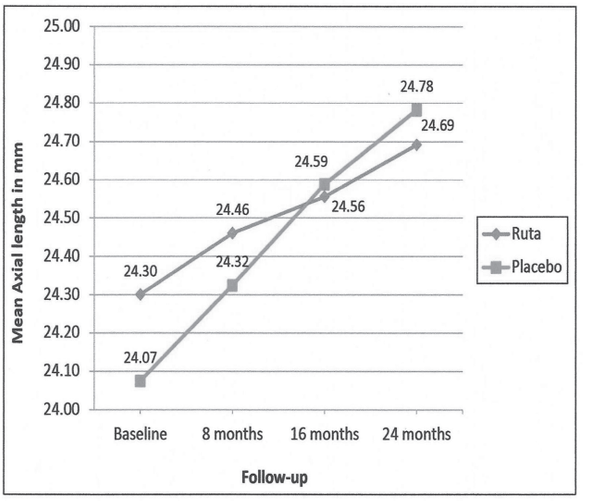

Figure 3 : Axial length in mm at different visits in two groups.

Grade of improvement based on primary outcome (SER) in two groups:

Changes in SER were graded with -0.75 D as cutoff point. Subjects with reduction, stabilization and slow progression of myopia of d" -0.75 D were categorized in maximum and moderate grade of improvement respectively. It was noticed in 47 (71%) subjects of Ruta-treated group, 10 (24%) in placebo group. so the overall benefit in Ruta versus placebo was 47%. Subjects who had myopia progression of > -0.75 to -1.0 D and > -1.0 D were categorized into mild and no grade of improvement respectively. Mild improvement

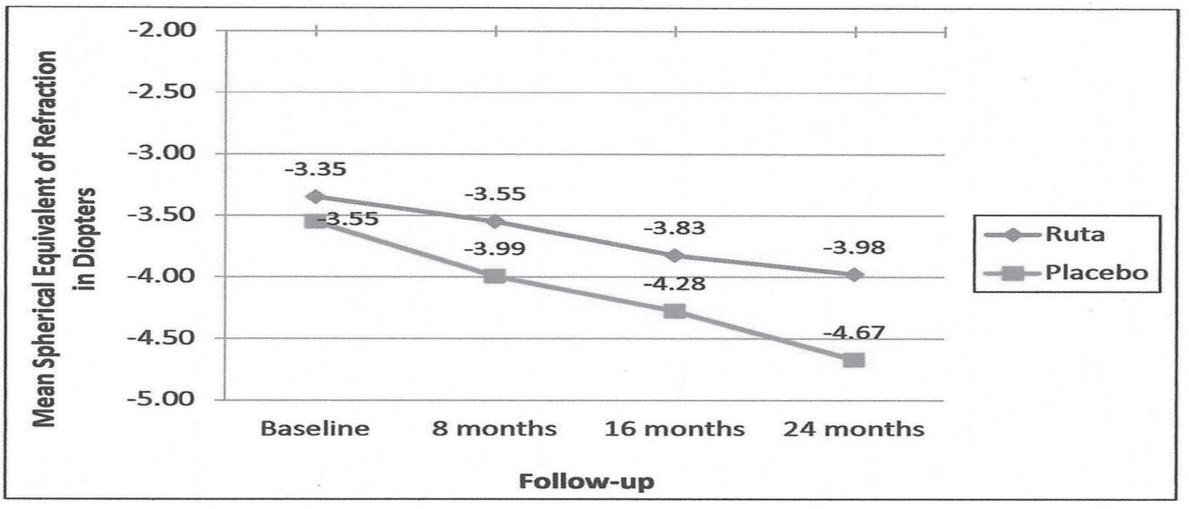

Figure 2 : Spherical Equivalent of Refraction in diopters at different visits.

was observed in 9 subjects of Ruta-treated group while 6 in placebo. Myopia progression of > 1.0 D was observed only in 10 subjects of Ruta-treated group whereas in 26 of placebo group (table 4).

Out of 66 subjects in Ruta-treated group, 47 (71%) were benefited whereas 19 were not benefitted. Subjects

Table 4 : Grade of improvement as per the change in myopia status after 24 months in two groups.

Grade of	Change in Myopia (SER)	Ruta	Placebo
Improvement	in Diopters	*n* (%)	*n* (%)
Maximum	Reduction	3 (5 %)	
	Stabilisation	1 (1 %)	
Moderate	Progression d" - 0.75	43 (65 %)	10 (24 %)
Mild	Progression > - 0.75 to - 1.0	9 (14 %)	6 (14 %)
No Improvement	Progression > - 1.0	10 (15 %)	26 (62 %)
	Total	**66 (100%)**	**42 (100%)**

benefited were majority of higher age group and had more near work activity as compared to those not benefitted. Majority of subjects benefitted had no parental history of myopia (table 5).

Table 5 : Subjects benefited and not benefited in Ruta-treated group and their baseline characteristics.

Baseline Characteristics	Benefited(*n* = 47)	Not Benefited(*n* = 19)	Total Subjects
Mean age (Years)	13.7	11.1	66
Mean Near work (Hours)	4.6	4.3	66
Gender, Females, *n* (%)	21 (65%)	11 (35%)	32
Gender, Males, *n* (%)	26 (76%)	8 (24%)	34
No parental myopia, *n* (%)	31 (79%)	8 (21%)	39
Parental myopia, *n* (%)	16 (59%)	11 (41%)	27

DISCUSSION

Key findings:

The results of this study has shown a statistically significant treatment effect of Ruta 3C of 0.49 D on controlling myopia and 0.32 mm on axial length as compared to placebo over 2 years. 71% subjects in Ruta-treated group had a slow progression of myopia of d" -0.75 D.

Possible mechanism of action:

Even though exact mechanism of development of myopia is not clearly understood, data from animal model and human studies has shown possible role of retinal defocus in development of myopia. In this study Ruta was found beneficial particularly in children of higher age group with more near work and with no parental myopia. While less benefit was observed in children of younger age with parental myopia. Hereditary myopia usually develops at a younger age and reduced scleral rigidity plays an important role in its etiology. So above finding shows that Ruta probably has acted on ciliary muscles rather than sclera and has achieved improvement in accommodation resulting

in proper focusing of image on retina during near work and thereby controlled myopia.

Comparison with other studies:

Results of Ruta were compared with different international myopia controlled studies such as *progressive addition lenses* (PALs) by Gwiazda, [24] *Pirenzepine* by Siatkowski [25] *Atropine* by Chua [26] Treatment effects on myopia were 0.20, 0.41, 0.92 D in PAL, Pirenzepine and Atropine study respectively. These findings show that Ruta has more controlling effect on myopia as compared to PALs and Pirenzepine.

Study of *Physostigma* on myopia by Basu has achieved a 67.7% visual improvement (> 1 line on Snellen's chart) within 6 months. However some lacunae such as results of this study were based on qualitative assessment of vision, with a study of short duration and it was a non-randomized, single blind study. So all these points give less validity to the study.

Reasons for dropout subjects:

3 subjects shifted to contact lenses were of higher age (17 to 23 years) and had no myopia progression. So the reason to go for lenses was cosmetic. One subject in Ruta group developed hypopigmentated patches over skin of face and chest after 1 month of medication. Detail history has revealed that this complaint was recurring for last 1 year, so patient was withdrawn from the study. 3 subjects in Ruta group were lost due to myopia progression. They were of younger age (< 11 years) with parental history of myopia so myopia progression was mainly under the influence of heredity.

Results of study were based on per protocol analysis :

In this study total 17 subjects were either withdrawn or lost to follow up. Out of these in 9 outcome measures were not available due to follow up of less than 6 months, while remaining 8 had a limited period of follow up of < 14 months. There was less chance of attrition bias because of a balance in baseline characteristics between two groups in retained subjects as well as between retained and total subjects within groups. Similarly there was no major difference in proportion of dropout subjects and their reasons for dropout between two groups.

Use of unequal randomization:

Ruta is a well proven drug since *Dr. Hahnemann's* time with its known pathogenic action and being used in practice for many years to treat different aliments. However there was no published study of Ruta on myopia. So its action on myopia has to be evaluated with the help of subjective and objective tests. So to get more information about effect of Ruta on myopia, an unequal randomization with more number of subjects were allocated to Ruta group. Second reason, in a placebo controlled study, more the number of subjects in treatment group than placebo, lesser will be the ethical issues. *Mr. Pocock*, a biostatistician has shown in many cases that there is only a minor loss of statistical power using randomization ratio even up to 3:1.[27] So in this study an unequal randomization with allocation ratio of 3 : 2 between Ruta and placebo group was used.

Use of Ruta in 3C (low) potency:

Myopia is a disease localized to a single organ (eye) with only organ symptoms and is *associated with changes in structure and shape of eyeball* that are irreversible. Ruta was prescribed by taking into account its p*articular effect on ciliary muscle and sclera* so it was considered as an organ remedy. They support the weaker organ and are usually given in lower potency, divided doses, repeated frequently. [28] Myopia is usually hereditary in nature and this genetic predisposition makes an individual susceptible to develop myopia with near work. Ruta was prescribed with an intension *to palliate or reduce daily ocular stress* and not used as a constitutional medicine. So by taking into consideration above points Ruta was used in low potency in the study.

Strength of study:

1. It was double-blind, randomized, placebo-controlled study, which is considered as a gold standard to study the efficacy of a drug to get an unbiased treatment effect.
2. There was homogeneity in baseline characteristics in retained subjects between two groups as well as between total and retained subjects within group after attrition. So there was a less chance of attrition bias in the results of study.

Limitations of study:

1. There was less sample size in this study as it was carried out in a single center.
2. Randomization was unequal between Ruta and placebo group. So results of study may have a less validity as compared to studies with equal allocation ratio.
3. Analysis of study was based on per protocol method so there are chances of false positive results of Ruta on myopic subjects.
4. Results of this study can't be generalized, as this study did not involve subjects of all age groups, different races, contact lens users.

Recommendations for future studies:

A multi-centric double blind randomized controlled study of Ruta in large number of subjects is required to confirm its efficacy and safety. Cessation of Ruta treatment for at least 1 year is necessary to know long term effect of Ruta on myopia. Use of Ruta in different dose will help to find its optimum dose for controlling myopia.

CONCLUSION

This study shows the efficacy of homoeopathic Ruta graveolens 3C on controlling ocular refraction and axial length as compared to placebo over 2 years. So Ruta can be considered as a better alternative in the treatment of simple progressive myopia.

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