DOI 10.5935/0034-7280.20170006

Phenylephrine 10% mydriatic effect: comparison between self instillation of eye drop in open eyes and spray in closed eyes

Efeito midriático da fenilefrina a 10% na comparação entre a autoinstilação de gota em olhos abertos e a vaporização em olhos fechados

Arlindo José Freire Portes[1], Anna Carolina Silva da Fonseca[2], Camila Monteiro Ruliere[2], Luiz Felipe Lobo Ferreira[2], Nicole Martins de Souza[2]

ABSTRACT

Objective: *To compare the effectiveness of phenylephrine 10% applied by a spray onto the eye closed over drop instillation onto an open eye on patients who will perform ophthalmoscopy and assess the level of difficulty and technical adequacy of the administration methods.* ***Methods:*** *The study was a clinical trial, controlled, randomized and paired, performed in 2014, involving 100 eyes of 50 patients in the Polyclinic Ronaldo Gazolla - RJ, with no ocular or systemic diseases that compromised the pupillary dilation. Patients underwent 10% phenylephrine eye drop instillation onto one open eye and spray application onto the other eye, which was closed. Pupillary diameter was measured before application and 10, 20, 30 minutes after. The process of instillation or vaporization was observed for its technical correctness by one of the authors. A questionnaire was asked to the patient about the difficulty of both methods after topical administration.* ***Results:*** *The average mydriasis difference between the eye groups assessed at a given time was at most 0.3 mm, which was not clinically or statistically significant (ANOVA: $F = 1.97$ and $p = 0.163609$). However, over time, the difference between the average pupil diameter before application and after 30 minutes was 1.15 mm to vaporized eyes and to 1.58 mm in eyes instilled with drops (ANOVA: $F = 129,22$ and $p \leq 0.0001$). Sixty per cent of patients touched the tip of the eye drop bottle onto the eye, while 12% touched the tip of the vaporizer with their fingers ($p < 0.000001$). Seventy two percent (72%) considered the drops instillation easy or very easy, while 62% considered vaporization in a closed eye easy or very easy ($p = 0.238$).* ***Conclusion:*** *The instillation of drops phenylephrine 10% in open eyes and the vaporization onto closed eyes showed similar clinical efficacy. Vaporization was safer and a little more difficult than instillation, despite the patients being experienced for instilling drops and inexperienced to vaporize the medication in a closed eye.*

Keywords: *Administration, topical; Ophthalmic solutions/administration & dosage; Phenylephrine; Eye/drug effects*

[1] Ophthalmology Service, Policlínica Ronaldo Gazolla, Universidade Estácio de Sá, Rio de Janeiro, RJ, Brazil.
[2] Academic Course in Medicine, Universidade Estácio de Sá, Rio de Janeiro, RJ, Brazil.

The authors declare no conflicts of interests.
Received for publication 17/10/2016 - Accepted for publication 23/11/2016

Resumo

Objetivo: Comparar a eficácia fenilefrina a 10% aplicada pelo próprio paciente por vaporização em olho fechado em relação à instilação de gota em olho aberto em indivíduos que irão realizar exame de fundoscopia e avaliar o nível de dificuldade e a adequação técnica entre os métodos de administração. **Métodos:** Ensaio clínico controlado, randomizado e pareado realizado em 2014 envolvendo 100 olhos de 50 pacientes na Policlínica Ronaldo Gazolla - RJ, sem doenças oculares ou sistêmicas que comprometiam a dilatação pupilar. Os pacientes foram submetidos à instilação de 1 gota de fenilefrina a 10% e aplicação de vaporizador do mesmo midriático no olho contralateral. O olho em que se instilou o colírio permaneceu aberto, enquanto o olho vaporizado ficou fechado durante as aplicações da medicação. O diâmetro pupilar foi medido antes da aplicação, 10, 20 e 30 minutos após. O processo de instilação ou vaporização foi observado quanto a sua adequação técnica por um dos autores. Após o processo foi perguntado ao paciente questões pré-formuladas sobre a praticidade de ambos os métodos. **Resultados:** A diferença de midríase média entre os grupos de olhos avaliados em um determinado tempo foi no máximo 0,3 mm , o que não foi clinicamente ou estatisticamente significativo (ANOVA: $F = 1,97$ e $p = 0,163609$) . Porém, ao longo do tempo, a diferença entre o diâmetro da pupila no tempo inicial e no tempo de 30 minutos foi 1,15 mm para os olhos vaporizados e 1,58 mm para os olhos instilados com gotas (ANOVA: $F = 129,22$ e $p \leq 0,0001$). Percentual de 60% dos pacientes tocaram a ponta do frasco de colírio nos olhos, enquanto que 12% tocaram o orifício na ponta do vaporizador com os dedos ($p < 0,000001$). Setenta de dois por cento (72%) consideraram a instilação de gotas fácil ou muito fácil enquanto 62% consideraram a vaporização em olho fechado fácil ou muito fácil ($p = 0,238$). **Conclusão:** A instilação de gotas em olhos abertos e a vaporização de olhos fechados da fenilefrina a 10% apresentou eficácia clínica semelhante. A vaporização foi mais segura e apresentou nível de dificuldade um pouco maior do que a instilação, apesar dos pacientes serem experientes para instilar gotas e inexperientes para vaporizar a medicação em olho fechado.

Descritores: Administração tópica; Soluções oftálmicas/administração & dosagem; Fenilefrina; Olho/efeitos de droga

Introduction

Spraying is a therapeutic route often used in medicine for the prevention and treatment of various diseases. Antihistamine medications, steroids, mast cell membrane stabilizers, anticholinergics, among others are released by nasal spray in order to treat allergies or congestion due to rhinitis or sinusitis[1,2]. Agents for sun photoprotection or temporary skin substitutes that form impermeable dressings may also be applied by spraying on the skin.[3,4]

In ophthalmology, there are lubricating sprays commercially available in several countries, for application both with eyes open or closed. There are few studies demonstrating the efficacy of medications when topically sprayed in the eye. The droplets of the ophthalmic solution are placed under pressure between the eyelashes and when the patient opens the eyes, they blend into the tear chamber.[5]

A recent study found that the fluorescein released by ocular vaporization reaches concentrations in the anterior chamber, but in a lower amount than would be reached by the instillation of drops[6]. Portes et al. reported in 2012 that the mydriasis produced by drops of tropicamide 1% was similar to that from spraying the same substance into the eyes. However, the amount of tropicamide released at each spray was twice that found in 1 drop of this said substance.[7]

The use of the medication applied at a distance by spray it with the eyes previously closed can facilitate the treatment in adult or elderly patients with: high ametropia (which make it difficult to see the bottle of eye drops properly); blepharohematoma (which makes palpebral opening difficult and makes the touch of the fingers sensitive to the skin of the eyelids); in elderly patients with motor coordination difficulties and in patients presenting with emotional discomfort at instillation.[7]

After extensive literature review in databases like Scielo, LILACS and MEDLINE, the authors have not found studies on the mydriatic effectiveness of phenylephrine 10% by spraying in eyes closed.

The objectives of the present study were:

a) to evaluate by serial measurements by pupilometry the mydriasis produced by the topical application of phenylephrine 10% by spray in the closed eye or instillation of drops in the open eye.

b) to make a comparative evaluation with a questionnaire about which topical application was more difficult.

c) to evaluate by observation of self-instillation which method was best suited

Methods

The survey was carried out from September to November 2014 at the Ophthalmology service of Policlínica Ronaldo Gazolla, Universidade Estácio de Sá, Campus Arcos da Lapa – RJ. A controlled, randomized clinical trial was conducted in a series of 50 patients to which phenylephrine 10% was instilled as drops in one eye, while the other was sprayed in the eyelid with the eye closed.

Patients were invited to participate in the study at their arrival for the ophthalmoscopy exam in the ophthalmology ambulatory at clinic of Policlínica Ronaldo Gazolla on Thursdays.

The eyes were chosen for the administration of eye drops or spray according to a pseudorandom number Excel table prior to application. The pupillary diameter was measured before the instillation and 190, 20 and 30 minutes after it in both eyes with a manual pupilometer "PD-meter".

A bottle of eye drop of a mydriatic ocular solution of phenylephrine 10% and a vial coupled to a vaporizer were used.

All patients had no ocular or systemic diseases that could affect the pupillary diameter.

Exclusion criteria:

1) Anisocoriasis and/or any change of pupillary diameter

2) Presence of any systemic disease affecting the autonomic nervous system.

3) Presence of posterior synechiae

4) Presence of inflammatory ocular diseases.

5) Presence of ocular disease preventing the measurement of the pupillary diameter

Methods of application: all patients remained seated during the study and were requested to look forward.

The eye drop was applied in one of the eyes, always in the same way and as follows: The patient was requested to direct the head backwards, extending the neck and looking up. The lower

eyelid was slightly drawn to expose the inferior conjunctival sac fundus. Then 01 drop of eye drops was self-instilled at the inferior sac fundus.

The spray was made in the eye where the eye drop was not applied, as follows: the patient was requested to remain seated, looking foward, and then to position the bottle so that the hole in the sprayer was in front of the eyelashes approximately 2 cm away from the eye of the patient, and the drug was sprayed only once with the lids closed. This whole process was done with dexterity and speed. The patients were requested to keep the sprayed eye closed for up to 10 seconds after instillation of the drop or spray. The bottle used was plastic, 7 cm high and 2 cm wide, with a volume of 7 ml. Each spray released an averaged 0.1 ml of ophthalmic solution, which corresponded to approximately 2 drops of eye drops in a circular dispersion area of 5.5 cm in diameter (measures taken on filter paper). This bottle vial was not available for commercial use with medications, so it was sterilized in ethylene oxide prior to the study, and then phenylephrine 10% was introduced into this bottle in sterile form.

After 30 minutes of the last pupillary diameter measurement, if the patient complained of ocular discomfort he underwent biomicroscopic examination to discard any corneal alteration, and the eyelids were also ectoscopically examined to rule out any sensitivity in the area of dispersion of the sprayer.

The instillation process or spray was followed by one of the authors.

After the process, the patient answered pre-formulated questions about the practicality of both methods. Administration-related aspects were observed and classified by the authors (Annex 1).

The database was created using the program Epi info 7. The test of "Wilcoxon signed rank" was applied to questions 4 and 5 of the questionnaire. Student's t-test for 2 paired samples was applied to questions 11 and 15, and the binomial test for two proportions of questions 8, 9, 10, 12, 13, 14. The ANOVA test for two factors with replicated measurements compared the results of mydriasis between the eyes in the several times after instillation. Statistical calculations were made by calculators from the website: "vassarstats.net".

This research was submitted to and approved by the Research Ethics Committee of Universidade Estácio de Sá (CAAE: 29365414.2.0000.5284). All participants signed an informed consent form.

Results

The average age of the patients was 64.4 years with a standard deviation of 12.38. Sixteen (32%) patients were men and 34 (68%) were women. 56% of patients were referred to ESF-Lapa/RJ, and the others were private or had health insurance.

Table 1 shows the mean mydriasis of each eye at corresponding time intervals from the beginning of instillation. It can be observed that the mean pupillary diameter and the standard deviation are very similar for each group. There were no clinically significant differences in the measurements (Table 1).

The analysis of variance (ANOVA) with two factors for repeated measurements showed F = 1.97 and p = 0.163609 when comparing the measurements between the groups of spray and drops. However, when we compared the groups in relation to time, F = 129.22 and p d" 0.0001. Therefore, the difference of the measures between the groups of spray and drops at each time was not statistically significant, but the difference of mydriasis of the groups between different times showed statistical significance.

Table 1
Mean pupillary diameter in the groups studied after instillation or spray of phenylephrine 10%

Time/Pupillary diameter	Pupils and drops Média	Standard deviation	Pupils and spray Média	Standard deviation
Before the application	4.25 mm	0.58	4.38 mm	0.66
10 minutes	4.68 mm	0.66	4.69 mm	0.74
20 minutes	5.21 mm	0.83	4.96 mm	0.70
30 minutes	5.83 mm	1.01	5.53 mm	0.86

The mean mydriasis difference between the groups of eyes evaluated at a given time was at most 0.3 mm, which is not clinically significant. However, over time, the difference between the diameter of the pupil in the initial time and the time of 30 minutes was at least 1.15 mm (clinically significant).

Seventy-two percent (72%) considered the instillation of drops easy or very easy, whereas 62% considered the spray in closed eye easy or very easy. The difference between the groups was not statistically significant (p = 0.238) according to the "Wilcoxon signed rank" test.

Three (6%) of the patients reported that they had difficulty in target the bottle of eye drops so that the drop hit the eye, and one (2%) always blinked during instillation. Nine (18%) patients said they had difficulty in targeting the sprayer to reach the eyelid margin, 5 (10%) that it was hard to squeeze the sprayer, and 2 (4%) that it was hard work with one eye closed. Forty-five patients (90%) did not report any particular difficulty to instill eye drops, and 32 (64%) to spray the eyes.

In 92% of individuals, the drop instilled fell in the eyes. In 90% of patients, the spray fell on the eyelid margin. Twenty-six percent repeated the drop instillation, whereas 40% repeated the spray. There was no statistically significant difference between the number of repetitions of drops in relation to the spray according to the binomial test (p = 0.0425).

The average drops applied by eye was 1.5, and the average was of sprays was 1.46 (p = 0.8036). Sixty percent of patients touched the tip of the bottle of eye drops in the eye, whereas 12% touched the tip of the sprayer with the fingers (p < 0.000001). The difference between the touch of eye drops in the eye tissues and the exit hole of the sprayer with the fingers was statistically significant.

Discussion

The efficacy of phenylephrine 10% was clinically similar to the two routes of topical administration tested. According to the ophthalmic literature, the maximum mydriasis caused by the substance tested occurs between 20 and 30 minutes of initial topical administration. The eyes tested showed the biggest mydriasis 30 minutes after vaporization or instillation.[8]

The average pupil dilatation was 1.15 mm for the eyes sprayed, and 1.78 mm for the eyes instilled with drops of phenylephrine 10%. Portes et al. [7] found average pupil dilatation of 2.35 mm for the eyes sprayed, and 2.48 mm for the eyes instilled

with tropicamide 1%. Dilation by tropicamide tends to be greater than that caused by phenylephrine 10%. However, it is greater when the two medications are used together sequentially, resulting in synergistic effect.[7,8]

Van Rooij in 2015 compared penetration in the anterior chamber of fluorescein instilled by eye drops on the ocular surface in relation to the spray of the same substance with the eye open. The amount of active principle found in the anterior chamber was about half of the observed after instillation of eyedrops. In this study, the values of the mydriasis found were too close between the groups, but the amount of phenylephrine sprayed amounted was equivalent to 2 drops of phenylephrine instilled. The fact that the spray was done about 2 cm from the eyelash also contributed to the good absorption of the mydriatic.[6]

Most patients instilled drops erroneously, touching the tip of the bottle in eye tissues and around the eyes in order to facilitate the topical administration, stabilizing the product bottle. The touch promotes contamination. The patients did not report difficulties to keep the bottle stable at a distance while spraying. Thus, there was no touch between the sprayer and the eye tissues.

Although the difference perceived between the level of difficulty in spraying in relation to that of drop instillation was small and not statistically significant; there were many more difficulties reported for spray than for droplet instillation. All patients had experience in instilling eye drops and had no experience in spraying their eyes. The training effect in the use of the sprayer could make it easier to use this route of administration in relation to instillation of eyedrops.

Annex 1

Questionnaire - Perception of ocular self-instillation of drugs:
Comparison between drops applied with and without face support device

1. Number of medical report: _____

2. Initial letters of the name: _____

3. Age: _____

4. Regarding the instillation of eye drops, you consider it:
1) Very easy ( ) 2) Easy ( ) 3) Neither easy nor difficult ( ) 4) Diffcult ( ) 5) Very difficult ( )

5. In relation to spraying in closed eye, you consider it:
1) Very easy ( ) 2) Easy ( ) 3) Neither easy nor difficult ( ) 4) Diffcult ( ) 5) Very difficult ( )

6. In relation to topical administration of eye drops, did you have any difficulties? ( ) Yes ( ) No.
If so, which ones? _____

7. In relation to spraying in closed eye, did you have any difficulty? ( ) Yes ( ) No.
If so, which ones? _____
Note:
In relation to the eye drop:

8. Did the drop instilled fall in the eye? ( ) Yes ( ) No.

9. Was it necessary to repeat instillation so that it fell in the eye? ( ) Yes ( ) No.

10. Did the tip of the bottle touch the eyelashes or the eyelid or the eye? ( ) Yes ( ) No.

11. How many drops were applied? _____
In relation to spraying in closed eye:

12. Did the application reach the palpebral margin? ( ) Yes ( ) No.

13. Was it necessary to repeat? ( ) Yes ( ) No.

14. Did the tip of the sprayer touch your fingers? ( ) Yes ( ) No.

15. How many applications were made? _____

References

1. Djupesland PG. Nasal drug delivery devices: characteristics and performance in a clinical perspective—a review. Drug Deliv Transl Res. 2013;3(1):42-62.
2. American Academy of Allergy, Asthma & Immunology. AAAI Allergy & Asthma Medication Guide [Internet]. [cited 2016 Oct 14]. Available from: https://www.aaaai.org/conditions-and-treatments/treatments/drug-guide/nasal-medication.
3. Monteiro EO. Filtros solares e fotoproteção. Rev Bras Med. 2010; 67(esp. 6):5-18.
4. Ferreira MC, Paggiaro AO, Isaac C, Teixeira Neto N, Santos GB. Substitutos cutâneos: conceitos atuais e proposta de classificação. Rev Bras Cir Plást. 2011; 26(4):696-702.
5. Craig JP, Purslow C, Murphy PJ, Wolffsohn JS. Effect of a liposomal spray on the pre-ocular tear film. Cont Lens Anterior Eye. 2010;33(2):83-7.
6. van Rooij J, Wubbels RJ, de Kruijf WP. A new spray device to deliver topical ocular medication: penetration of fluorescein to the anterior segment. J Ocul Pharmacol Ther. 2015;31(9):531-5.
7. Portes AJ, Barbosa AC, de Mello GL, Lopes MA, Cavalcanti RS. Tropicamide 1% mydriatic effect: comparison between spray in closed eyes and eye drops in open eyes. J Ocul Pharmacol Ther. 2012;28(6):632-5.
8. Pavan-Langston D, Dunkel EC. Handbook of ocular drug therapy and ocular side effects of systemic drugs. Boston:Little Brown; 199. Mydriatics and cycloplegics. p.226-33

Corresponding author:
Arlindo José Freire Portes.
E-mail: freireportes@hotmail.com