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Technical Evaluation of Eye Drops Instillation: A Systematic Review

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Abstract: Objective: Assess the profile of eye drops in patients with eye diseases. Methods: Studies available in the scientific literature were identified without any time limits using the databases Embase-Medline, Scielo, Scopus and Web of Knowledge. The selected studies were compared with the following inclusion criteria: (i) if the study evaluated the eye drop instillation, (ii) if the study involved participation of patients with eye diseases. Results: Twelve studies met the inclusion criteria. Of them, 83.33% evaluated the technique of eye drop instillation in patients with glaucoma, 8.33% in patients with eye diseases and 8.33% in patients with cataract after undergoing surgery to correct. 41.66% of studies have chosen to record a video of patients to analyze the technique of instilling eye drops and 41.66% did not describe the/esearch location. Regarding the type of study, 75% had the design as prospective cross-sectional, 8.33% prospective open label study, 8.33% intervention study and 8.33% study called masked trial. Although studies evaluate the technique of eye drop instillation, only 8.33% describe in the article the reference in the literature used to evaluate patients. 50% of articles acknowledged some sort of bias or limitation. Conclusion: The limitations inherent in these types of studies should guide future research.

Key words: Eye drop instillation, eye diseases, ophthalmic solutions.

1. Introduction

Worldwide, low visual acuity and blindness problems are highly prevalent, with a negative impact on quality of life and adverse consequences both individually and collectively. According to WHO (the World Health Organization), the leading causes of chronic blindness include cataract, glaucoma, macular degeneration, corneal opacities, diabetic retinopathy, trachoma and eye diseases in children [1]. The NEI (National Eye Institute) reports that among the American population over 40 years (142, 648, 393) about 25.85% will carry diabetic retinopathy, cataracts, glaucoma and macular degeneration related to age [2].

Although the estimates and the data presented, about 80% of cases of blindness in the world can be prevented or treated through medical interventions or use of medicinal products [3]. Regarding the use of medication, one must pay attention to the time, the strength and the proper administration of drugs. According to WHO, the irrational use of medicines is a global health problem, in which more than half of all prescription drugs dispensed and are used inappropriately [3].

Medication errors can occur at any stage of pharmacotherapy, ranging from prescription to administration of the drug to the patient, accounting for approximately 65-87% of all adverse events [4].

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Higuchi et al. [5] reported that the correct use of medicines has potential value for adherence to drug therapy.

Among the administration techniques of pharmaceutical forms, instillation of eye drops deserves special attention, since the correct administration of these is essential for a positive prognosis of diseases affecting the eye. This happens because, unlike medical treatments based on drug oral intake, the correct use of eye drops depends on a administration technique based on fine motor movements [6]. According Tatham et al. [7] inadequate eye drops instillation may lead to treatment failure, unnecessary use of medicines and can cause eye infection due to contact of eye drops with eye region.

Although the literature mentions these precautions, there is no standardization in the use of eye drops throughout the world, which requires further investigation on this subject. In this respect, this systematic review aims to evaluate different methodologies employed in research on the use of eye drops for patients with eye diseases.

2. Methodology

2.1 Search Strategy and Selection Criteria

At first, the available studies in the literature were identified without temporal limitations using databases Embase, SciELO, Scopus, Lilacs, Pub Med and Web of Science as bibliographic data source. For this purpose, a search with the terms MESH was performed in the following combinations: (“ophthalmic solutions”) AND (“administration, ophthalmic”) (“ophthalmic solutions”) AND (“instillation, drug”), (“administration, ophthalmic”) AND (“instillation, drug”), (“ophthalmic solutions”) AND (“administration, ophthalmic”) AND (“instillation, drug”). Subsequently, in order to complement and broaden the search, specific descriptors were used in the following combinations: (“ophthalmic solutions” OR “eyedrops”) AND (“administration, ophthalmic” OR “medication administration”), (“ophthalmic solutions” OR “eyedrops”) AND (“instillation, drug”), (“administration, ophthalmic” OR “medication administration”) AND (“instillation, drug”), (“ophthalmic solutions” OR “eyedrops”) AND (“administration, ophthalmic” OR “medication administration”) AND (“instillation, drug”).

The selection process was performed in three steps (title, abstract and full text) by two reviewers. The titles and abstracts were compared with the following inclusion criteria pre-established to determine the relevance of the topic: (i) if the study evaluated the eye drop instillation, (ii) if the study involved participation of patients with eye diseases. Comments, editorials, articles that were not in Portuguese, Spanish and English or items that were not available in its entirety were excluded.

2.2 Statistical Analysis

The SPSS version 17.0 was used for the calculation of kappa statistic to check the agreement in the selection of studies included among authors, decreasing the chance of losing some study and the possibility of bias [5].

For the extraction and construction of data on the characteristics of the articles included in the study, a table that allowed the identification, study duration, study location, year of publication, sample, methodology, instrument used in the article and results was used (Tables 1 and 2).

2.3 Assessment of the Methodological Quality of the Selected Studies

The methodological quality of observational studies included was assessed according to the STROBE recommendations [8]. Strobe protocol features 22 essential items that must be described in observational studies. Those items that each article followed were analyzed so that later were calculated the total percentage of recommendations implemented, thus obtaining the score percentage of Strobe for these studies.

Table 1 General characteristics of the studies included in the review.

Study	Country	Duration of study	Local	Sample size	Limitations	Percentage score of the Strobe for observational studies
Ritch et al., 2003	USA	Not described	Not described	20	Cross-sectional study, disabling the monitoring of patients; It presents bias with respect to self-reported; lack of patients include different levels of vision impairment; lack of assessment regarding the counseling effect on the correct use of eye drops.	Does not apply
Vaidergorn et al., 2003	Brazil	2 months	Ambulatory	47	Not described	68.18%
Lisboa et al., 2007	Brazil	3 months	Not described	40	Not described	72.72%
Ikeda et al., 2008	Japan	12 months	Teaching hospital	27	Not described	63.63%
Stone et al., 2009	USA	Not described	Private room	139	Not described	63.63%
Hennessy et al., 2010	USA	8 months	Not described	204	Video recording performed only once; different drops the size of that used by the patient; failure to evaluate the performance in patients with Parkinson's disease or arthritis; lack of assessing patients at different stages of the disease.	72.72%
Hennessy et al., 2011	USA	12 months	Not described	409	Video recording performed only once; different drops the size of that used by the patient; failure to evaluate the performance in patients with Parkinson's disease or arthritis; lack of assessing patients at different stages of the disease.	68.18%
Sleath et al., 2011	USA	Not described	Private room	102	Study only in one place.	77.27%
Gupta et al., 2012	INDIA	4 months	Teaching hospital	70	Failure to assess the socioeconomic status of patients; nervousness in the act of instilling due to the presence of the doctor; failure to include patients with physical limitations	77.27%
Schwartz et al., 2013	USA	3 months	Not described	164	Patients chose in which eye could administer the eye drops; search location; questionnaire based on the patient’s memories	86.36%
Angela et al., 2014	Canada	Not described	General hospital	54	Not described	54.54%
Miguel al., 2015	France Portugal	5 months	Polyclinic and teaching hospital	25	Not described	77.27%

Table 2 Methodological description of the articles included in the systematic review.

Study	Type	Methodology	Results
Ritchet et al., 2003	Interventional study	Patients were instructed to a new technique of instillation, guided through the procedure. All measurements were then repeated.	The average number of drops used decreased from 0.1 ± 0.6 drops (p = 0.60, paired t-test, ranging from -2 drops -1). The accuracy of drop placement increased from 80.0% to 82.5% (p = 0.32, paired t test).
Vaidergornet et al., 2003	Prospective cross-sectional study	Each participant performed a diurnal curve before and another after explaining the correct instillation of eye drops. Then, the average IOP (intraocular pressure) obtained was compared.	There was a significant decrease of 22.3% in mean intraocular pressure. Of the remainder, 35 (38.9%) eyes showed a slight decrease (-8.2%) in their average blood pressure, and 20 (22.2%), a slight increase (8.4%), both were not statistically significant.
Lisboa et al., 2007	Prospective cross-sectional study	A cross-sectional study of 40 patients with glaucoma under clinical treatment with eye drops to use. A questionnaire was applied by performing observations of instillation. The following variables were investigated: sex; education; age; socioeconomic conditions; hand washing; number of drops; motility disorders; person applying eye drops; application site; eye drops tip contact with the eyelids, conjunctiva and cornea; previous instruction; applying position; burning, pain or eye irritation after application and visual acuity. From the questionnaire and the observations, the variables were correlated with the quality of instillation. The analysis model was binary logistic regression.	It was found 40 patients, of whom 24 (60%) were enrolled in Group 1 (poor instillation), of which 16 (40%) in group 2 (suitable instillation). Among all the variables in question were statistically significant for proper instillation the person to apply the drug, itching and irritation
Ikeda et al., 2008	Prospective cross-sectional study	The patient instillation technique was evaluated based on the proximity of the tip of eye drops with eyes, the application position of the eye drops, eyelid closure, treatment (removal) excess liquid and nasolacrimal occlusion.	Multivariate analysis revealed that the factors that influence the control of intraocular pressure to a lower value of 21 mmHg, with topical medication were: application of drops in the center of the eye and removal of excess fluid, as well as gender and age. Suitable home topic application was dependent on the patient's understanding of the disease and knowledge of the correct technique of application.
Stone et al., 2009	Prospective open label	Included were 139 patients with a diagnosis of glaucoma and ocular hypertension who had used one or more topical ocular hypotensive medications for at least six months and their instilled drugs themselves. A video was recorded to assess the patient's performance for instilling eye drops.	Patients had relatively good performance in the instillation of eye drops. One hundred and twenty-nine of the 139 patients (92.8%) reported no problem to manage their eye drops, and 86 of 139 (61.9%) believed that never lost a drop by instill eye drops in the eye. The proportions of patients who were only able to instill a drop on the eye without touching the tip of eye drops to the ocular surface was 14 of 64 patients (21.9%) with a 15 mL eye drop to 36 of 117 (30.8%) with a 2.5 mL eye drop
Hennessy et al., 2010	Prospective cross-sectional study	Patients completed a survey on the use of eye drops. To evaluate the eye drops instillation technique was recorded a video in the act of instillation was asked the patient to perform the same act as he performs at his home, using a 5 mL eye drops.	Seventy-one percent of individuals were able to instill a drop in the eye, of these only 39% instilled a drop in the eye without touching the eye surface, instilling an average of 1.4 ± 1.0 drops, using 1.2 ± 0.6 attempts. Of the 142 individuals who denied touching the drops on the ocular surface, 24% touched the ocular surface with drops.
Sleath et al., 2011	Prospective cross-sectional study	Eye drops application evaluation through video.	Eighty percent of the patients instilled eye drop successfully on the first try. Thirty-four percent of patients touched the bottle in the eye or eyelashes. Only 38% of patients perfectly the drops instilled throughout the study.

(table 2 continued)

Study	Type	Methodology	Results
Hennessy et al., 2011	Prospective cross-sectional study	Patients with glaucoma or ocular diseases with a visual acuity of 20/60 in one eye or both to significant loss of visual field. Subjects were observed through recorded video.	409 individuals were included (205 glaucoma, retina 204). Among the individuals who put a drop on the eye without touching the eye surface, there was a tendency for glaucoma patients get better performance, although both groups had poor results (success, 39% glaucoma vs. 31% retina, p. 0.09).
Gupta et al., 2012	Prospective cross-sectional study	The following parameters were evaluated: time to instill the first drop, the number of drops instilled, the site of contact, any contact with the tip of the eye drops and eyelid closure or tear duct after instillation.	The average time required to install the first drop was 14.8 ± 3.7 seconds (8.7 to 23.5 s range). The average number of drops used for the collyrium instillation was 1.8 ± 1.2 drops (range, 1-8 drops). In 22 patients (31.43%), the drops fell on the eyelids or cheeks. Fifty-three patients (75.7%) touched the tip of the eye drops in the globe or periocular tissue. Twenty patients (28.57%) closed their eyes after instilling drops and 4 patients (5.7%) occlusion of the lacrimal punctum. Only 6 patients (8.57%) were able to correct instillation of eye drops (instilling a drop and instill into the conjunctival sac without contact with the tip of the bottle)
Schwartz et al., 2013	Masked trial	Patients were selected by randomization and observed for 12 weeks. At baseline, patients were given a questionnaire for self-assessment of the difficulty with eye drops administration. Patients were evaluated in the study beginning with visits in the 1st week, 4th week and 12th week. At baseline and at 12 th weeks, patients demonstrated instillation of eye drops using a lubricant eye drops.	Of 164 patients enrolled, 50% had been previously treated with ocular hypotensive medication for 3 years. Only 11.4% of patients reported difficulty with eye drop administration at baseline. At baseline, 18.2% of patients touched the tip of the bottle into her eyes and 10.3% did not hit the eye by instilling the drops. At 12 weeks, 18.5% and 8.6% of patients, respectively, had similar difficulties. In general, the difficulty with the instillation of the solution was observed in 42.1% of patients. Difficulty in both visits was observed in 35.3% of patients who reported difficulty at the beginning and in 17.2% of patients who denied difficulty.
Angela et al., 2014	Prospective cross-sectional study	Cataract patients who underwent surgery were recruited on the day after surgery. Data were collected using a standardized questionnaire self-report, reviewing medical records and footage of patients who administered the drops in the operated eye. Two independent observers assessed objectively instillation technique. Predictors were assessed using the OR (odds ratio) for a logistic regression model.	The study involved 54 patients. Subjectively, 17 patients (31%) reported difficulty in instilling the drops. Sixty-nine percent reported always wash their hands before using the eye drops, 42% believed that never lost a drop by instilling in the eye and 58.3% believed that never touched their eye with the tip of the bottle of eye drops. Objectively, 50 patients (92.6%) had improper administration technique, including not hit the eye by instilling eye drops (31.5%), not instilled the correct amount of drops (64.0%), contaminating the tip bottle (57.4).
Miguel et al., 2015	Prospective cross-sectional study	A prospective observational study was conducted in patients with advanced glaucoma and vision loss. Data were collected for 5 months and then applied questionnaires (demographic issues, quality of life, self administration of eye drops and adherence to treatment) and were carried out interviews and recordings of video tasks (self administration of eye drops, reading, up and down stairs, wandering in tight spaces and uneven floors). Held ophthalmologic evaluation with record pre-defined form and researched the correlation between visual field defects and limitations of patients	25 participants obtained a total 12 hours of video. All patients reported being able to put the hypotensive eye drops and 68% said they have never failed in instilling eye drops. However, 20% failed to instill a drop in the eye. Seventy-two percent (72%) patients reported never touch the bottle in the eye, but 40% said they play. There was moderate difficulty in activities, especially when walking in areas with obstacles and uneven floors. Some patients had proprioceptive mechanisms of adaptation to low vision (as grope the step with the foot). There was a correlation between the severity of visual field defects and limitations in most activities.

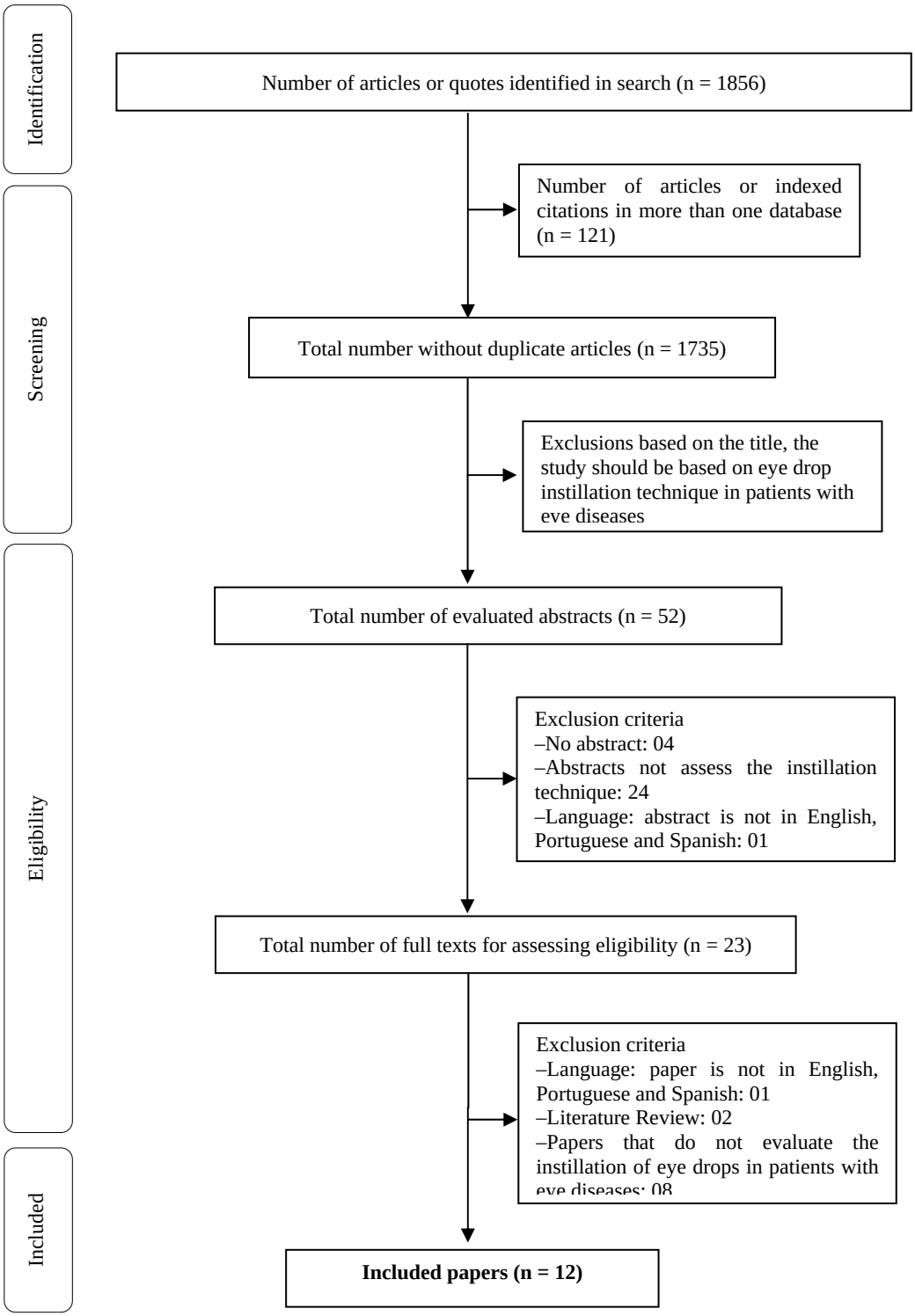

Fig. 1 Flowchart in accordance with PRISMA.

2.4 Quality Review

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Statement PRISMA (Fig. 1) [9]. This statement provides essential information on the methodology and development of systematic reviews, as follows: terminology, research question formulation,

identification of studies and data mining, study's quality, risk of bias by combining data (plus selective study) or publication bias results.

3. Results

The initial screening made with the terms: ophthalmic solutions, administration, ophthalmic, instillation, drug, medication administration and eye drops allowed the identification of 1,856 articles, of which 121 were linked in more than one database (Fig. 1). After exclusion of repeated articles, 52 were considered potentially relevant and had their abstracts analyzed. At this stage, the degree of agreement between the two raters was substantial, k = 0.904. Abstracts examined, 23 were selected for evaluation of the full text. At the end of the article selection process, only twelve met the specific criteria Japan (1), India (1), Brazil (2), United States (6) Canada (1), Portugal (1).

Of the twelve articles analyzed, ten assessed the eye drops instillation technique in patients with glaucoma, one assessed the instillation technique in patients during the postoperative cataract and one study evaluated the instillation technique in patients with eye diseases, not being restricted only to glaucoma.

Among selected articles, five chose to record video of the patients to analyze instill drops technique and the other used only observation for evaluation. Five studies did not describe the search location and the duration of trials ranged from three to twelve months. Regarding the size of the sample there was a large variation between studies analyzed with a minimum of 10 and maximum 409 patients.

For the design of the study it was observed that nine studies were prospective cross, an intervention study, one masked trial, one prospective open label study and only one study was not described his design (Table 2).

Among the articles that assessed instillation of eye drops technique, only one article described the literature reference used to evaluate patients. In regard to limitations stated in the articles, it was noted that seven recognized some sort of bias or limitation in the research.

Regarding the observational studies, the studies followed Strobe statement ranging from 54.54% to 86.36% of the items listed by the Protocol (Tables 1 and 2).

4. Discussion

Despite the search in various databases, few studies have been found on the theme. This shows that although the theme is relevant both for scientific research and for professional practice, the literature is still incipient in this regard. Thus, conducting studies that focus on the aspects involved with eye drops administration technique should be encouraged, as influential accession strategy and increased effectiveness in patients using these medicines.

Good part of the analyzed studies did not mention the practice scenarios where they were performed [10-14]. The literature suggests that research should be communicated in a transparent manner so that readers can follow the methodology and draw clear conclusions. Moreover, the credibility of research depends on the thorough assessment of the strengths and weaknesses of the study design [5]. In this context, informing the search location is critical, since this can affect the results of the study.

Also in terms of scenario, most of the studies analyzed used the hospital/ambulatory to evaluate the technique of eye drops instillation. Literature data show that health professionals working in hospitals and outpatient clinics are more likely to work as a team to achieve relationships of trust with the patient [15,16] which explains the evaluation of the use of eye drops in these scenarios. Stevenson and colleagues reported that the integration of health professionals in the hospital allows, through a combination of specialized and complementary skills, the achievement of efficient results, benefiting the patient [17]. On the other hand, when analyzing the selected studies, the results may be biased by the fact that patients are in places such as hospitals and clinics, which stimulates the correct use

of eye drops, in contrast to the way in which they would use in their homes.

The selected studies in this review found high variation in sample size and the absence of sampling calculations. Small samples can hamper the detection of positive results, especially when the tools used to measure have low sensitivity [18]. The sample size planning is often important and almost always difficult to execute, requiring careful when choosing the scientific objectives and to obtain appropriate information before the beginning of each study. This is a very important step in the validation of data in a particular scientific study, in addition to ethical and economic issues [19].

Most studies were observational, however when evaluating the manuscripts, none fully followed the items suggested by Strobe protocol for the development of observational studies. The protocol provides recommendations on what should be included in observational studies for a more complete and clear description. Despite the Strobe was not used as a tool to assess the methodological quality of studies, it use its recommendations to corroborates the methodological quality of the research [8].

Most studies have chosen to assess the instillation technique drops through the video, this media technique can bring better understanding of the information provided and may assist in the evaluation to contribute in reducing the time spent by those applying [20]. Therefore, the use of video is relevant in health education area of patients with eye diseases, since it allows further analysis of the technique by the patient.

Most of the articles analyzed assessed the instillation technique of eye drops, specifically in patients with glaucoma. This occurs because patients with chronic disease have adherence problems to treatment [21]. According to the same author, this behavior may be influenced by factors such as knowledge about the disease, proper technique of instillation and the cost of pharmacotherapy. Therefore, it is essential study the use of eye drops techniques to avoid possible adverse effects, increasing the effectiveness of pharmacotherapy and promoting the best prognosis.

Although papers evaluate instillation technique drops in patients with eye diseases, studies in almost its entirety, do not mention the literature used as reference to evaluate the technique [10-13, 21-26]. According Vaidergorn et al., and Fraunfelder et al. [27, 28]instillation should be performed sitting or lying down, instilling eye drops only a single drop without contact from the bottle end with the ocular tissues. After instilling the eyes must remain closed for at least two minutes.

Although the technique described, the articles exhibit variability in the number of instilled drops at instillation when evaluating patients. The lack of a standardized technique for evaluating the instillation of eye drops may hamper evaluation or comparison with other researchers [29, 30]. According to Whiting et al. [30] to validate the diagnostic test, it is necessary to compare with the gold standard, in order to validate the test investigated.

5. Conclusions

In terms of methodological quality this review showed that no study has fulfilled the recommendation STROBE criteria. An important intervention in the design of research in this setting is associated with the increase in size of its samples, providing greater statistical power and allowing the realization of systematic reviews and meta-analyzes in order to improve the research methodology. This can increase the quality of the evaluations of aspects related to the use of eye drops by patients with eye diseases. In addition, the studies showed no standardized and validated administration techniques, stressing the need to broaden the discussion on the use of eye drops within the multidisciplinary guidelines.

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