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A systematic review and meta-analysis on the efficacy of topical povidone iodine in adenoviral conjunctivitis

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ABSTRACT

Purpose: To evaluate if topical povidone iodine (alone (PI) or combined with dexamethasone (PI-DXM)) is superior to placebo for treating adenoviral conjunctivitis (AC).
Methods: A systematic review was performed according to Preferred Reporting Items for the Systematic Review and Meta-Analyses (PRISMA) Statement. An electronic search was made of PubMed, Embase and Cochrane Library. Randomized control studies that compared PI or PI-DXM with placebo were included. At least three researchers were involved in all phases. Primary outcomes were AC duration and the number of clinical resolutions during the first week. Secondary outcomes were conjunctival redness and serous discharge one week after starting treatment and the rate of AC complications.
Results: Only five studies met the inclusion criteria. PI-DXM reduced the duration of the disease by 2.4 days (IC95% 4.09–0.71), however this result was based only in one study. PI and PI-DXM did not modify the probability of clinical resolution during the first week; relative risk (RR) = 1.77 (IC95% 0.63–4.96) and 1.70 (IC95% 0.67–4.36). The impact of PI on the probability of pseudomembranes could not be estimated. PI-DXM did not influence the risk of developing subepithelial infiltrates RR = 0.73 (IC95% 0.02–3.38).
Conclusions: At this time there is great uncertainty about the usefulness of PI on the course of adenoviral conjunctivitis. PI-DXM may have a small effect on AC duration. To make future reviews possible, it is important to standardize the way in which these results are reported. Futures studies should include etiological confirmation, unit of study (eyes vs patients) and report on those aspects that are more relevant for patient quality of life (duration of the disease, development of complications: pseudomembranes and subepithelial infiltrates).

1. Background

Adenoviruses are one of the most common causes of infectious conjunctivitis. Their name derives from their initial isolation from human adenoids in 1953 [1]. These are medium-sized icosahedral, non-enveloped, double stranded DNA viruses and form part of the Adenoviridae family. Infections with adenoviruses are a significant source of morbidity and mortality world-wide and at all ages, through readily transmittable infections at mucosal sites, causing an array of diseases including conjunctivitis, gastroenteritis, hepatitis, myocarditis, and pneumonia [2]. They are considered one of the main causes of infectious conjunctivitis [3].

These viruses can induce severe ocular inflammation. Patients usually refer tearing, foreign body sensation and photophobia. Clinical findings include eyelid edema, conjunctival hyperemia, chemosis, follicular reaction, corneal involvement in the form of keratitis. In some cases, severe inflammation can lead to the formation of inflammatory conjunctival membranes [4]. If untreated, these membranes become incorporated into host tissue and can form scars that may restrict eye movement (symblephara) and/or cause symptoms of dry eye [5]. Some serotypes of these viruses have the potential to infect the entire ocular surface including the corneal epithelium, and induce the formation of corneal subepithelial infiltrates (CSI). These infiltrates most commonly resolve within a few weeks of onset, but can persist for years in a significant proportion of patients, and in some cases they may leave permanent visual loss due to corneal scarring [5].

In the postpandemic period, a clear reduction in the incidence of conjunctival infections, especially adenoviral conjunctivitis, has been

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reported. This is probably due to social distancing and to the hygienic measures adopted to prevent SARS-Cov-2 transmission [6]. Nevertheless, Adenoviruses have been considered the most common cause of acute viral infection of the conjunctiva, accounting in some series for up to 75% of the cases of conjunctivitis [2,3]. Outbreaks in different institutions are common, resulting in costly losses of productivity. In particular, nosocomial viral conjunctivitis are common, and outbreaks in ophthalmology units may impose restrictions on clinical practices. The sum of direct and indirect costs of each episode of conjunctivitis was estimated in 2020 as high as $669, with direct costs increasing by $467 with each additional infected family member. Being a ADVC such a common condition this means that these infections constitute a significant economic burden [2,7].

In one recent retrospective study conducted in a tertiary hospital, Palomero de Arriba et al, estimated that pseudomembranes appeared in 20% of patients with adenoviral conjunctivitis. In this study, pseudomembranes were present for more than a week and nearly 40% of patients who developed pseudomembranes had at least one corneal complication. For instance in this study, 17% of the patients who developed pseudomembranes also developed subepithelial infiltrates [8].

Despite the clinical and economic impact of adenoviral infections, no treatment has proven to modify the natural history of adenoviral conjunctivitis [9]. Nevertheless, in the last years several studies have suggested that povidone iodine (PI) may have a beneficial effect in these ocular infections [10].

PI is composed of diatomic iodine and polyvinylpyrrolidone (povidone). PI is a water-soluble polymer that serves as a carrier for iodine. Iodine oxidizes water to release ions that directly act on bacterial, viral or fungal membrane proteins to microbicidal effect [10]. There is a great deal of experience with PI in ophthalmology. Its utility in the prophylaxis of endophthalmitis during ophthalmic surgery and in the prevention of ophthalmia neonatorum has been well established [10]. More recent research suggests that PI may also be useful in the treatment of other infections such as bacterial keratitis [11].

The aim of this systematic review is to evaluate the impact of topical PI (alone or combined with DXM) on the natural course of adenoviral conjunctivitis; specifically, its ability to reduce disease duration and the risk of developing complications such as pseudomembranes or subepithelial infiltrates.

2. Materials and methods

This systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations (https://www.prisma-statement.org, accessed on 1 April 2021). The project was registered in Prospero in November 2020 (registration number: CRD42020220197).

Participants in the selected studies are patients that were diagnosed of adenoviral conjunctivitis in one or both eyes. Patients with both clinical and microbiological diagnoses were included.

Trials in which topical PI (ocular drops), alone or combined with dexamethasone were compared with placebo (artificial tear or the vehicle) were included. There is not consensus on which is the optimal concentration of PI. Thereby PI concentration was not considered an inclusion criteria. The following comparisons were considered in this review: 1. PI versus control. 2. PI + DXM versus control. Studies in which the intervention consisted of one isolated irrigation with a PI solution at the time of diagnosis were excluded.

The following outcomes were considered:

Primary outcomes:

- AC duration in days
- Number of AC resolutions at day 6/7.

Secondary outcomes:

- Clinician graded conjunctival redness one week of starting treatment.
- Free of serous discharge one week of starting treatment
- AC complications (pseudomembranes or CSI).

In December 2020, an extensive search was performed in three major medical literature databases: PubMed, Embase, and Cochrane, for available studies, without languages restriction. Articles that compared PI or PI-DXM with placebo (vehicle or artificial tears) in adenoviral conjunctivitis were selected. Only randomized control trials were included.

The Science Citation Index was used to find studies that cited the identified trials. Investigators of the included studies were contacted to identify additional published and unpublished studies. The search strategy in PubMed was: *((viral conjunctivitis AND povidone iodine) OR (viral conjunctivitis AND povidone-iodine) OR (adenoviral conjunctivitis and povidone iodine) OR (adenoviral conjunctivitis and povidone-iodine) OR (("Povidone-Iodine"[Mesh]) AND "Adenoviridae Infections"[Mesh]) AND "Conjunctivitis"[Mesh])) AND((randomized controlled trial[Title]) OR (*controlled clinical trial) OR randomized OR placebo OR (drug therapy) OR randomly OR trial OR groups)) *NOT (*experimental animals/not humans) and was adapted to Embase, and Cochrane. The references of the articles were used as a secondary source to complete the search and in December 2021 the search was updated. The selection process of the located articles is described in Fig. 1.

After gathering all the potential studies, all references were exported to Endnote, duplicates were eliminated, and candidate abstracts were screened by two of the authors. According to the inclusion criteria, a second selection was made through the complete text of the selected abstracts. During both phases, the selection was made by two of the authors (EGA and JZG), acting independently. At all stages, disagreement was resolved via consensus and discussion or, if necessary, through consultation with a third reviewer (J.G.M-M).

Two of the authors (JZG and EGA) extracted data using a standardized form, that contained 13 fields. Six of them were referred to characteristics of studies (study design, studied population, intervention, outcome measures, results, observations), while the remaining seven evaluated the risk of bias of the study, as recommended by the Cochrane manual [12]: bias arising from the randomization process (selection bias), bias in the allocation concealment (selection bias), bias in the blinding of participants and personnel (performance bias), bias in the blinding of outcome assessment (detection bias), bias due to incomplete outcome data (attrition bias), bias due to selective reporting (reporting bias) and finally other bias.

Data were independently extracted by both authors and compared. Disagreements were resolved by discussion, and data was transferred to Review Manager (Review Manager 5.4.1) by a third author (JGMM). The risk of bias of randomized clinical trials results was evaluated following the Cochrane risk-of-bias domains for randomized trials available in RevMan 5.4 [12].

For each outcome of interest, the summary result of the meta-analysis and results of individual studies were shown using forest plots. Heterogeneity among studies was assessed using I2. The risk ratio (RR) was used for dichotomous outcomes. When the outcome was continuous it was expressed as mean difference (MD) and standard deviation (SD) of the mean difference.

3. Results

The selection process is summarized in Fig. 1. All references were exported to Endnote and duplicates were eliminated. The list of the 55 non-duplicated publications was exported to Excel. Two of the authors (JZG and EGA) independently assessed the titles and abstracts and made the first selection. Full texts of articles deemed potentially eligible were then screened independently by each investigator for final inclusion. Of these 55 initial publications, sixteen were selected for idoneity

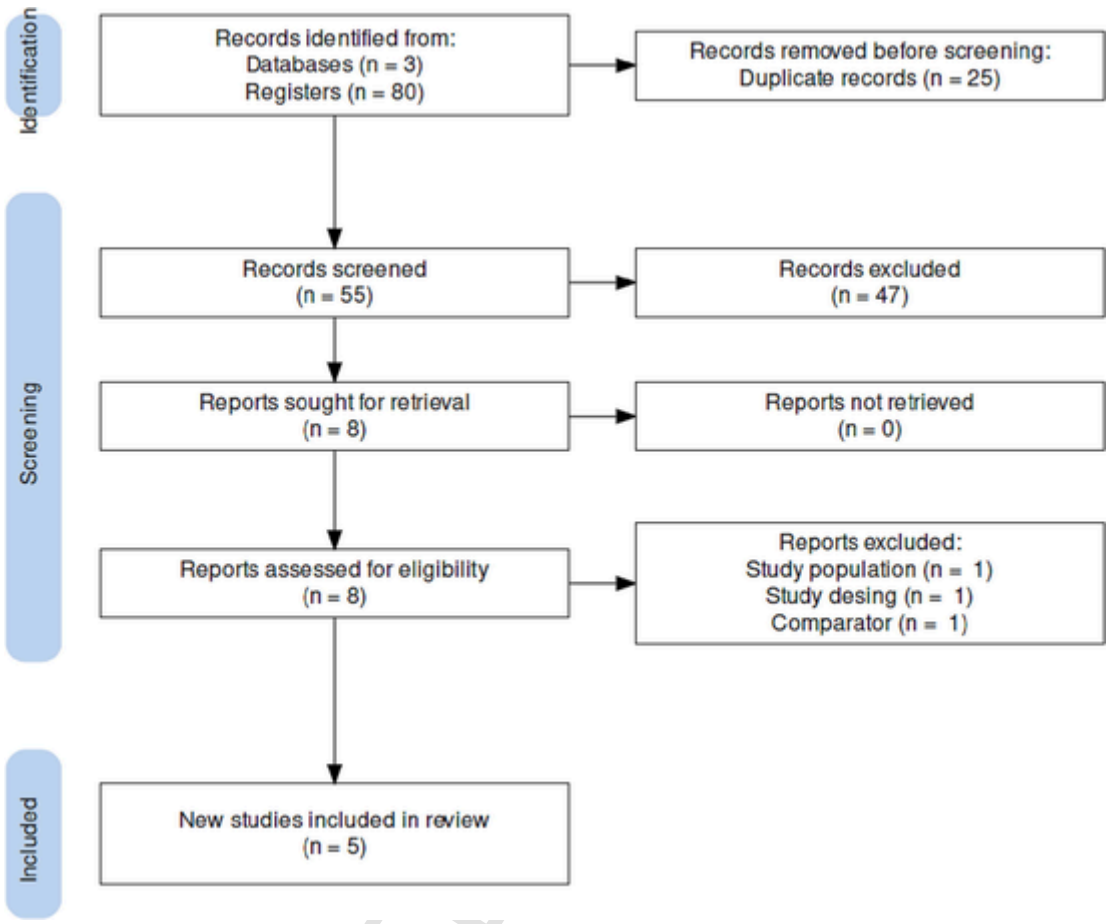

Fig. 1. Search results diagram: Studies identified by databases and registers.

based on abstract. Of these sixteen articles, eight were selected for idoneity after full text analysis. Of these eight articles, three were eliminated [13–15] (Fig. 1). Finally, the five articles that fulfilled the inclusion criteria were selected for the meta-analysis [16–20]. At all the stages, disagreement was resolved via consensus and discussion or, if necessary, through consultation with a third reviewer (J.G.M–M).

Below is a summary of the 5 trials included in this review. See Table 1 for detailed information on individual trials.

(1) PCR is done, but it is not an inclusion criteria.

These studies were conducted in Brazil, Israel, India, and Italy. All the selected works were randomized clinical trials that studied low concentrations of PI ranging from 0.4% in Pinto 2015 (Pinto, 2015) to 1% in Kovalyuk 2017 (Kovalyuk, 2017). In all the studies drops were administered 4 times a day, but within different periods of time. In Pinto 2015 [16] and Kovalyuk 2017 [17] drops were administered for a week. While in Pepose (Pepose 2018 and Pepose 2019) the treatment period was shorter (5 days) [18,19], and in Ricciardelli (2022) the duration of treatment was longer (20 days) [20].

Some trials included several branches with two experimental groups (Pepose 2018: one experimental group received PI 0.6%, while the second experimental group was treated with a combination of PI 0.6% and dexamethasone 0.1%) [18], while others included two control groups (Kovalyuk 2017 has three branches because it compares PI 1% with two control groups; one of them treated with placebo (hypromellosa 0.3%), while the second control group received dexamethasone 0.1%) [17].

The units of analysis differ in the selected studies. Kobalyuk 2017 [17], Pepose 2018 [18], and Pepose 2019 [19] studied eyes. Pinto, 2015 [16] and Ricciardelly 2022 studied patients [20]. The number of people included in each study ranges from 59 in Ricardelli 2022 to 178 in Pepose 2018.

These trials recruit people during the initial days of the infection. Disease duration is considered an inclusion criterium for most studies. Time from disease onset ranges from 3 days in Kovalyuk 2017 [17] to 7 days in Pinto 2015 [16]. In Ricciardelli 2022 disease duration does not seem to have been considered as an inclusion criterium [20].

The Kovalyuk 2017 and Ricciardelli 2022 studies required microbiological confirmation as an inclusion criterium [17,20]. In these studies, adenoviral etiology had to be confirmed by PCR. Kovalyuk et al found that adenovirus 8 was the most commonly involved serotype [17]. Nevertheless, in most studies diagnosis was made only on clinical grounds without any microbiological or serological confirmation. Pinto 2015 did not consider microbiological confirmation an inclusion criterium but made a subgroup analysis in the patients in which the adenoviral etiology was confirmed [16].

Three studies were excluded after evaluating the full-text report. The reason for excluding them is summarized in Table 2.

In brief, the Isenberg 2002 study was excluded because the control group did not meet the defined criteria [13], the Tunay 2014 study was excluded because it did not evaluate the intervention of interest [14], and the Yazar 2016 study was excluded because it was not a randomized control trial [15].

Isenberg 2002 [13] is probably the first modern study in which the viricidal effects of PI were tested in adenoviral conjunctivitis. The experimental group received PI 1.25%, while the control group was treated with a combination of three topical antibiotics (neomycin–polymyxin-B-gramicidin). In this study the diagnosis of viral conjunctivitis was made on clinical grounds. Adenoviral etiology was not confirmed but bacterial etiology was excluded using bacterial

Table 1
Characteristics of the selected studies.

Study, year, country	Diagnosis (Etiological vs clinical)	Disease duration criterium	US	Experimental group	Control Group	Outcome measures
Pinto 2015 Brazil	Clinical(1)	7 days	P	PI 0,4%-DXM 0.1 % (n = 61)	Tears(n = 61) (methylcellulose 0.5% with benzalkonium chloride) (BAC)	Duration of the disease (symptoms evaluated by ophthalmologist) SEI IOP Patients opinion on the usefulness of treatment
Kovalyuk 2017 Israel	Microbiological (PCR) (Diagnosed clinically and confirmed by PCR)	3 days	E	PI 1%-DXM 0.1% (n = 26)	DXM 0.1% (n = 26) Hypromellose 0.3% (preservatives?) (n = 26)	Rate of improvement in symptoms: Complete recovery (low titers of Adenovirus by PCR) and Speed of improvement Signs of adenoviral keratoconjunctivitis in treatment groups (clinical score): % of ISESymptoms (questionnaire) : reported by the patients at each visit.
Pepose 2018 India	Microbiological: Positive Rapid PathogenScreening (RPS) Adeno-Detector Plus	5 days	E	PI 0.6%- DXM 0.1% (n = 59)	PVP-I 0.6% (n = 59) Vehicle, no details (n = 58)	Clinical resolution Adenoviral eradicationAdverse events (safety)
Pepose 2019 Brazil	Clinical (suspected acute viral conjunctivitis) RPS in all, but not as an inclusion criteria (21 RPS + in each group) Only PCR in RPS+: 27 in PI group and 23 in vehicle group	5 days	E	PI 0.6%-DXM 0, 1% (n = 66)	Vehicle, no details (n = 66)	Clinical resolution at day 6 (ophthalmologist): absence of both bulbar conjunctival redness and serous conjunctival discharge.Viral status (only in studied patients: 27 in PI and 23 in vehicle) : The two treatment groups were not statistically different from each other in viral status at any visit.
Ricciardelli 2021 Italy	Microbiological: adenoplus and PCR	Not stated	P	PI 0,6% (n = 34)	Tears, with hyaluronate-based tear substitutes (n = 25)	Target: SEIs decrease or resolution, conjunctival chemosis and injection resolution, corneal transparency recovery

US = unit of study; E = eyes; P = Patients; PI = povidone iodine; DXM = dexamethasone; SEI = subepithelial infiltrates; IOP = intraocular pressure; PCR = polymerase chain reaction.

Table 2
Characteristics of the studies excluded during the eligibility phase (after analyzing full texts).

Study, year, country	Diagnosis (Etiological vs clinical)	US	Experimental group	Control Group	Reason for exclusion
Isenberg, 2002	Clinical(1)	E	PI 1.25%:	Neomycin–polymyxin B-gramicidin	The control group was treated with antibiotics. Different etiologies of conjunctivitis were included: bacterial and viral conjunctivitis
Yazar 2016	Not stated	P?	PI 0,5% (n = 66)	Trifluorothymidine (n = 66)	The work is described as a retrospective randomized study. The control group was treated with trifluorothymidine, not with placebo. It is not stated how the recovery was measured.
Tunay 2014	Clinical (2)	P	PI 2,5% irrigation + antibiotic + tears (n = 15)	Netilmisin + tears (n = 20)	Experimental and control group were treated with antibiotic (Netilmisin 0.3%) The intervention was a single irrigation with PI.

US = unit of study; E = eyes; P = Patients; PI = povidone iodine; DXM = dexamethasone; PCR = polymerase chain reaction.
(1) If both eyes were affected, only the right eye was included in the study.
(2) In some cases, swabs were used to exclude bacterial conjunctivitis.

cultures. This study was excluded because the control group received an intervention (a combination of three antibiotics) that may have some biological effect in some viruses.

The Tunay 2015 study was excluded from the analysis because this work studied a different intervention [14]. The study, published in 2014, investigated the effect of a single irrigation of PI at the time of diagnosis [14].

The Yazar 2016 study is described as a retrospective randomized study. After unsuccessfully trying to contact the authors to clarify this contradictory design, Yazar 2016 was excluded from the analysis [15].

Figs. 2 and 3 summarize the 'Risk of bias' assessment. Overall, the trials were considered to be at moderate to high risk for the main types of bias.

In all cases the studies are described as randomized trials, but in some only limited information is given about the randomization process and the allocation concealment. In three studies the randomization process was described but two studies did not describe the randomization process and were considered at unclear risk of bias. In Kovalyuk 2017 and Pinto 2015 the randomization process is described [17,16] while in Pepose 2018 and Pepose 2019 not enough information is reported about the randomization process [18,21]. In Ricciardelli 2022 [20], the randomization scheme was made using an online generator, but information about how allocation was concealed is not given. Similarly, in most trials the risk of bias during the allocation process is not clear. Attrition bias was low in Pinto 2015, Pepose 2018, Pepose 2019 and Kobalyuk 2017 and high in Ricciardielli 2021 in which 9 out of 68 participants did not complete follow up [16,18,21,17,20]. Selective reporting was moderate in most studies, including in most cases surrogate measures that were not initially defined as outcome variables.

Only Pinto 2015 reported information on the impact of PI drops on the duration of the disease [16]. This study showed a reduction of 2.4 days (IC95% 4.09–0.71) in the duration of the disease in the group of patients that was treated with PI, a statistically significant change. No other studies reported this important integrated outcome (Fig. 4).

Most studies reported several manifestations of the disease at different times. The rate of clinical resolution of infected eyes one week after

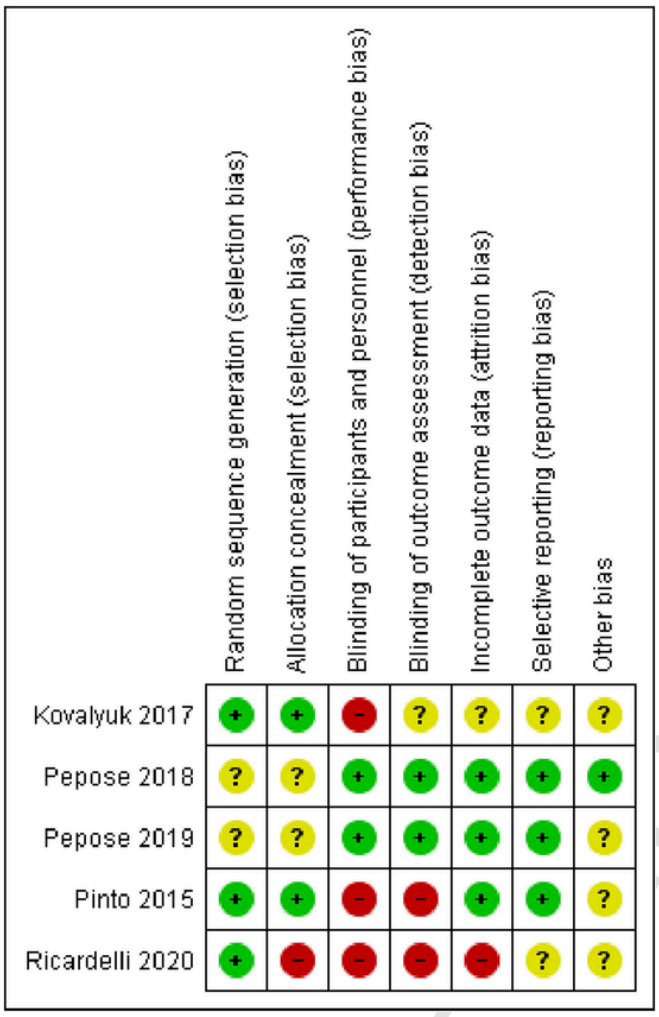

Fig. 2. Risk of bias summary: judgement of risk of bias for each included study.

starting treatment was reported in the Pepose, 2018 and Pepose, 2019 studies [18,21]. The unit of study in both cases were eyes. The analysis of this data could not demonstrate differences in the resolution at day 6/7 in patients treated with PI (1.77 (IC95% 0.63–4.96) or PI-DXM DXM 1.70 (IC95% 0.67–4.36) (Fig. 5 and Fig. 6).

An effect on the evolution of the most commonly reported symptoms could not demonstrated. The proportion of eyes free of conjunctival redness or watering was similar in the group treated with the combination of PI and DXM and the control group (Fig. 7 and Fig. 8).

Regarding complications of adenoviral conjunctivitis, available data did not allow for an analysis of the impact of PI or PI combined with DXM on the incidence of pseudomembranes. A significant reduction in the proportion of patients treated with PI who developed SEI was found (Fig. 9).

The combination of PI and DXM did not demonstrate any significant effect on the development of ISE (Fig. 10).

4. Discussion

Adenoviral conjunctivitis is one of the most common disorders seen in general and ophthalmic primary care, although recent reports suggest that anti-COVID measures have resulted in a significant reduction in the transmission of this infection during the last two years [6]. Despite the testing of different antiviral agents, none of them have been effective and the development of an effective treatment for AC remains elusive. Medical staff represent a high proportion of these cases [22]. Outbreaks among health workers constitute an important cause of sick leave, leading to important economic losses with the cost of each episode being estimated as high as $670 and increasing with each affected family member [7].

In 2021, a narrative review published by Dang et al showed significant uncertainty about the usefulness of this treatment [23]. A Cochrane review (that also included a meta-analyis) published one year later, studied the efficacy of several topical interventions (including PI) on viral conjunctivitis [24] and obtained similar results. However this revision failed to include some significant research, like Pepose 2018 and Pepose 2019 studies [18,19].

In our review, five studies were included. Overall, the risk of bias was moderate and the number of patients small. The analysis of the results suggest that PI may have a small effect on the natural history of AC, shortening the duration of the disease by 2 days (20%) and increasing the number of patients that are asymptomatic one week after the onset of the symptoms. Nevertheless, this conclusion is based on only one study that included a small number of patients (Pinto 2015). Most studies report on the influence of PI or the combination of PI in the presence of different manifestations of AC at different times. Using the available information, although the number of clinical resolutions at one week was higher in the group treated with PI, our analysis could not demonstrate a beneficial effect of standalone PI or the combination of PI and dexamethasone one week after the appearance of the conjunctivitis. The magnitude of the RR in both cases was similar (Figs. 5 and 6).

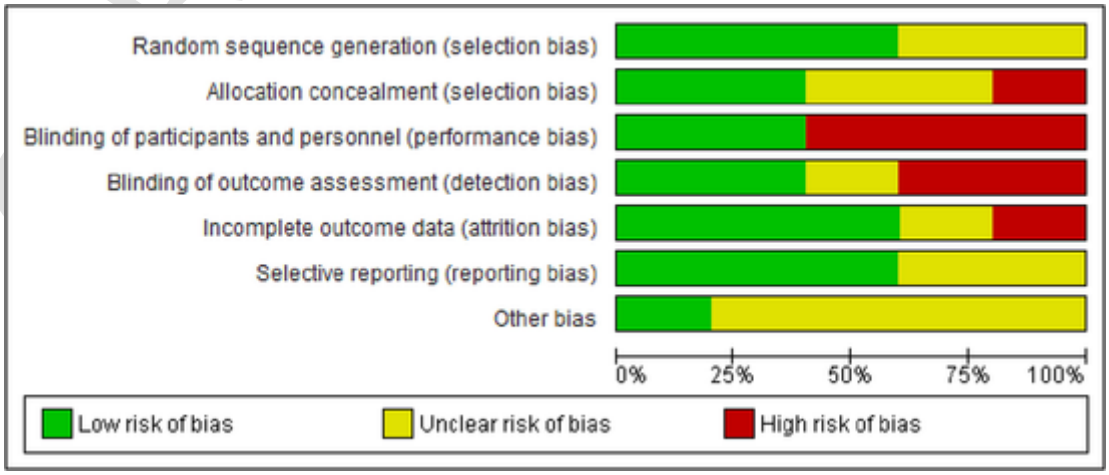

Fig. 3. Risk of bias graph: judgement of risk of bias presented as percentages for all included studies.

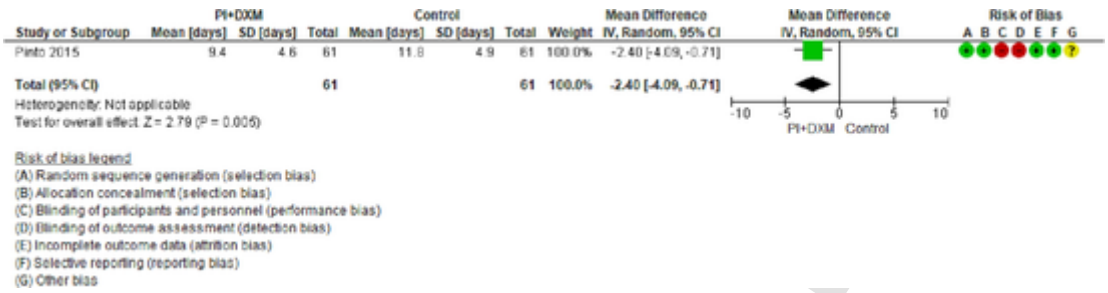

Fig. 4. Forest plot comparison of PI + DXM vs control: Adenoviral conjunctivitis duration (days).

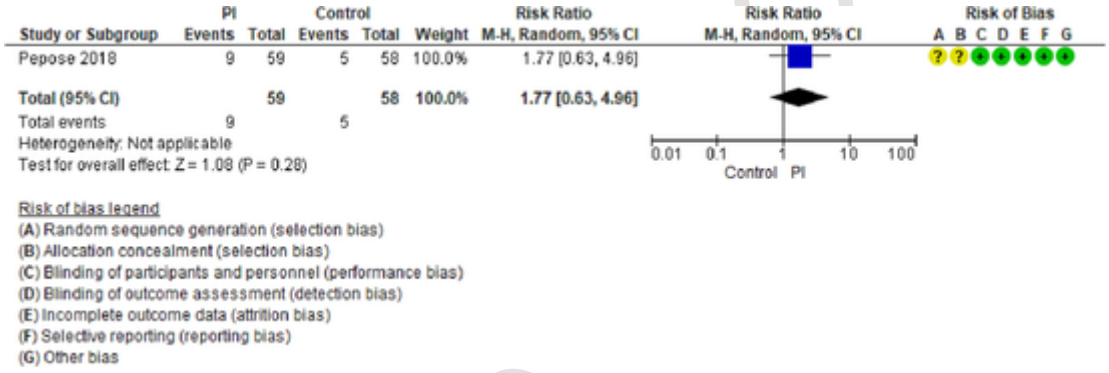

Fig. 5. Forest plot comparison PI vs control: Adenoviral conjunctivitis clinical resolutions at day 6/7 of starting treatment.

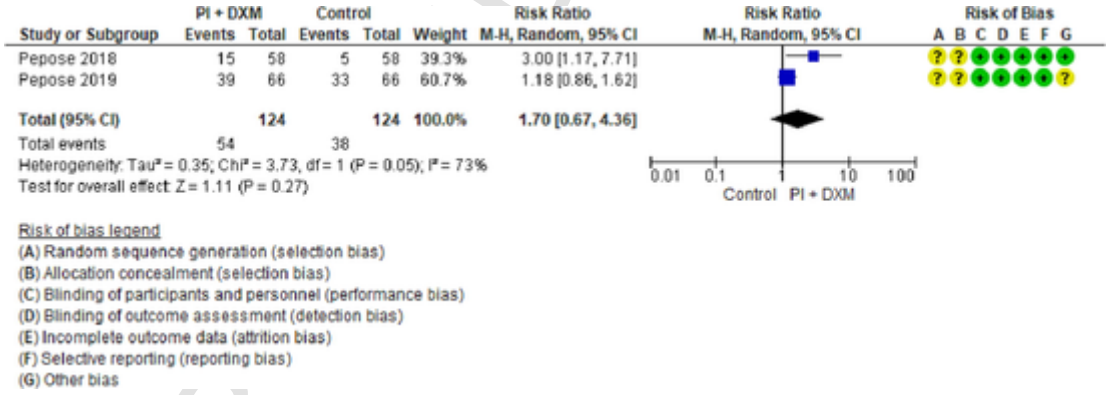

Fig. 6. Forest plot comparison PI + DXM vs control: Adenoviral conjunctivitis clinical resolutions at day 6/7 of starting treatment.

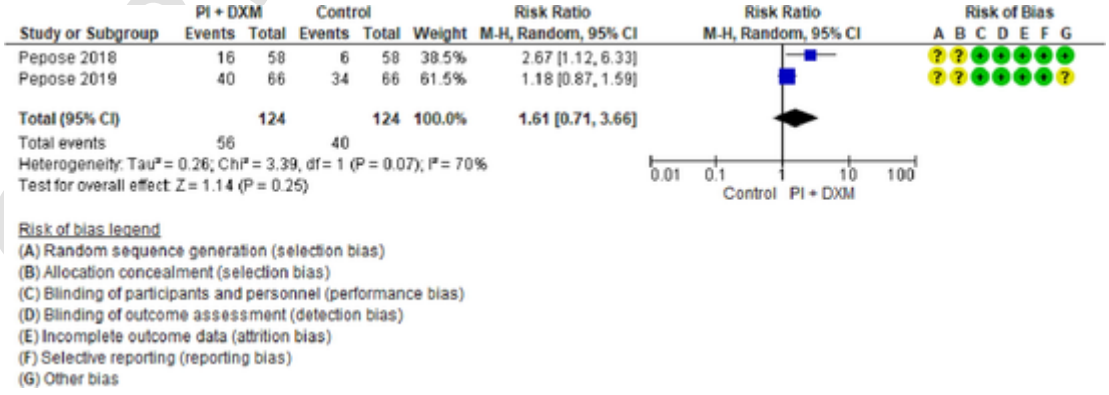

Fig. 7. Forest plot comparison PI + DXM vs control: Free of conjunctival redness one week of starting treatment.

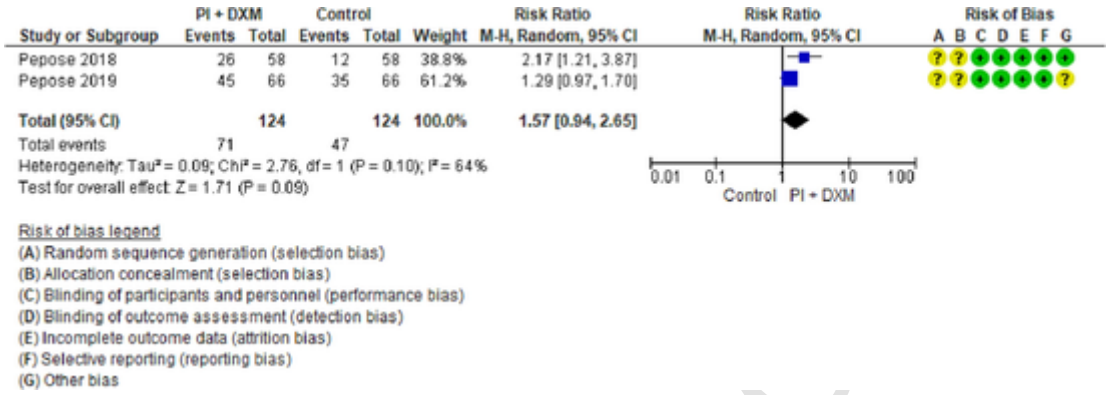

Fig. 8. Forest plot comparison PI + DXM vs control: Free of serous discharge one week of starting treatment.

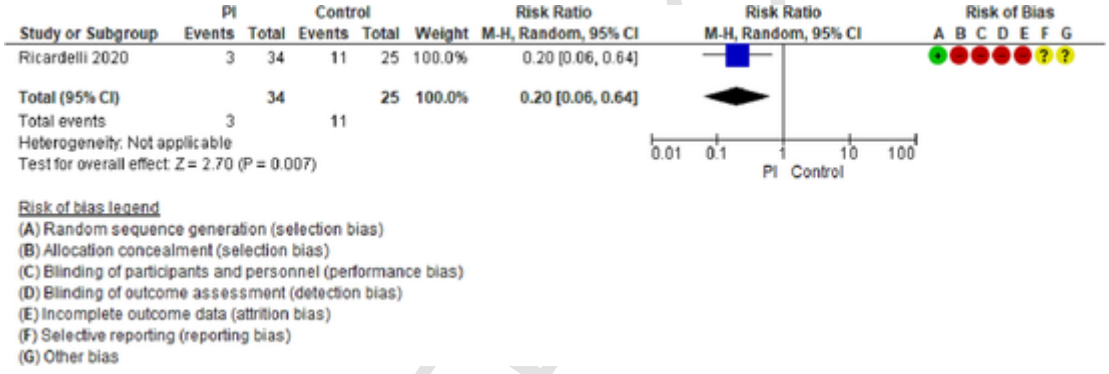

Fig. 9. Forest plot comparison PI vs control: Corneal Subepithelial Infiltrates development.

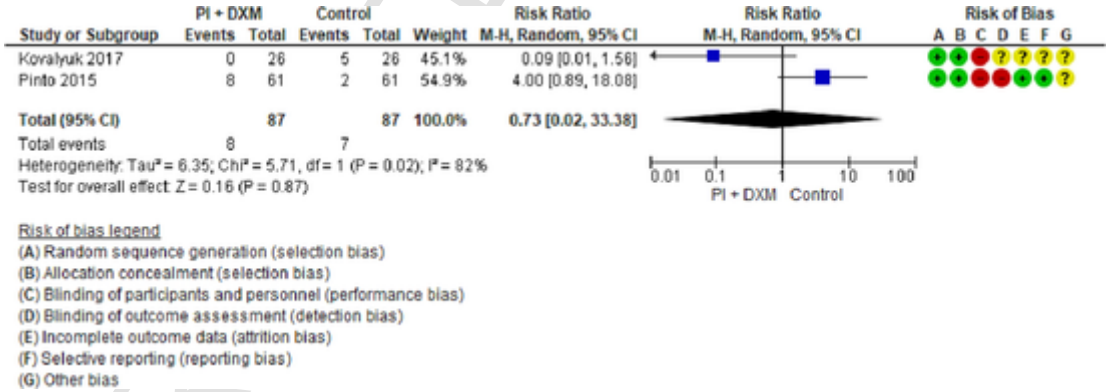

Fig. 10. Forest plot comparison PI + DXM vs control: Corneal Subepithelial Infiltrates development.

Regarding the impact of PI on the risk of complications the available data allowed an estimation to be made of the influence of PI and PI-DXM on the development of SEI but not on pseudomembranes. Standalone PI was associated with a significant reduction in the incidence of SEI. Nevertheless, this analysis should be taken with great caution because it is based on only one study with a very small number of patients and with a high risk of bias (Fig. 9) [20]. The combination of PI and DXM did not show a beneficial effect on the development of this complication. This analysis included two studies that found opposite results. While the study by Kobalyuk 2017 found a beneficial effect, Pinto 2015 found a detrimental effect [17,16].

One important design limitation is that many articles do not explain the unit of study. Conjunctivitis may affect one or both eyes, and when both eyes are affected, they may be related in a non-symmetrical and non-synchronic way. The units of analysis differ in the selected studies. While Kovalyuk 2017, Pepose 2018 and Pepose 2019 studied eyes, Pinto 2015 and Ricardielli 2021 studied patients.

Another important limitation is that AC diagnosis was clinical in most patients included in this review, without any etiological confirmation. Although it is true that AC has some distinctive attributes, such as the presence of follicles or adenopathies, these manifestations are not specific and other microorganisms can also produce follicular conjunctivitis. There is no universally accepted definition for adenoviral conjunctivitis and criteria vary among studies. If etiological tests improve it would be feasible to include etiological confirmation as an inclusion criterium in forecoming metanalysis. Nevertheless, at this time, most of the published studies do not consider microbiological confirmation as an inclusion criterium. Microbiological confirmation could be done using PCR as in Kovalyuk at al study [17] or an antigen detection test like in Pepose est al study [18]. These methods have different rates of sensibility and specificicty and can only detect a limited number of serotypes

of adenovirus. Thereby microbiological confirmation was not considered an inclusion criterium.

Blinding remains an important issue. PI has a brownish color and produces some itching, while the drops used by the control groups are colorless and do not produce any discomfort although one recent study demonstrated that successful masking can be achieved [25]. Nevertheless, even using opaque bottles, given the color of the solution and the itching it produces an observant patient can easily find out if they have been allocated to the experimental or the control group. Indeed, in the Pinto 2015 study itching was reported by a significantly higher proportion of patients allocated to the PI-DXM group. Only the use of an active brown placebo can overcome this important limitation.

The included studies were conducted in different countries where different serotypes may predominate over others and different serotypes of adenovirus may have different levels of virulence and different sensitivities to PI. Over 50 types of Adenoviruses (Adv) have been described [26]. Indeed, one recent in vitro study tested the resistance of 7 types of AdV to PI and found different antiviral activity among different serotypes, with types Ad 19/64 and Ad 37 being more resistant to PI [27]. Cultivating and serotyping AdV is expensive and complex, but the use of newly developed serological tests as an inclusion criterium may help to standardize the results in future studies. The inclusion of some cases of non-adenoviral follicular conjunctivitis and infections caused by different strains of adenovirus may explain the high degree of heterogeneity found in our analysis.

The chosen PI concentration could be another source of heterogeneity. A 5% concentration of PI is the accepted standard to prevent intraocular infection during cataract surgery. Nevertheless, more diluted concentrations seem to have stronger bactericidal, viricidal and fungicidal effect. There is no generally agreed or established optimal viricidal concentration; thus, another source of heterogeneity may be the use of different concentrations. In the included studies, concentrations ranged from 0.4% in the Pinto 2015 study to 1% in Kovalyuk 2017 [16,17]. The combination of PI with dexamethasone 0.1% in the experimental group also contributes to the high degree of heterogeneity observed in our analysis [17,16,18,21].

The composition of the drops given to the control groups may have also been a source of heterogenicity. Preservatives may have some antiviral activity. In Pinto study artificial tears containing benzalkonium chloride were used. This information regarding the preservatives contained in the solution that was administered to the control group is not detailed in the other four studies.

In summary, our study tried to determine the utility of povidone in adenoviral conjunctivitis, however the available evidence did not make it possible. Our results have important limitations, and the most significant aspect of our work is to highlight the difficulties in integrating published studies. Important outcomes for patients, such as the duration of the disease or the rate of membranes and CSE, are not reported in many studies. It is especially important to include the influence of any treatment on both aspects as they can have a significant impact on a patient's quality of life in the long term. Improving and harmonizing reporting would facilitate the integration of data for future meta-analyses. Thus, the main contribution of this article is to make some recommendations on how results should be reported to allow effective systematic reviews in the future:

Ideally, studies should include some kind of etiological confirmation.

For the sake of simplicity, the unit of study should be the eye. Including both eyes is confusing and forces investigators to use complex methods that take into account inter-eye correlation. Authors should report the time patients need to be completely free of symptoms. This outcome should be expressed in mean time (standard deviation) and median time (interquartile range). Another interesting parameter could be the number of patients that are completely free of symptoms at day 7, 14 and 21. Other parameters like redness, conjunctival staining, are subjective surrogate measures and do not have the value of time to resolution.

When PI treatment is started in the first days, it may prevent the spread to the contralateral eye (crossover infection). If only unilateral cases are included, the rate of bilateralization is easy to collect and has great clinical value. It also has value from an epidemiological point of view as it may be a proxy of viral load and disease contagiousness.

Complications have an important prognostic value. Pseudomembranes and ISE may have chronic repercussions on a patient's quality of life. Thus, all the studies should include the number of the patients that develop these complications.

PI has a brownish color and produces some itching, while artificial tears and the vehicle are colorless and do not produce itching. The use of active placebos in the future may help the conceal allocation.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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