Pilocarpine treatment of Sjögren's syndrome curative effect of meta-analysis of randomised controlled trials

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Abstract

Objective

Recent research has increasingly focused on improving symptoms in patients with Sjögren's syndrome (SS). This study aims to evaluate the efficacy of oral pilocarpine in treating SS, synthesising the latest scientific evidence from randomised controlled trials (RCTs).

Methods

We systematically searched PubMed, Embase, the Cochrane Library, and the Science Citation Index for relevant randomised controlled trials (RCTs) published up to November 2023. Cochrane is used to assess the quality of literature studies and to extract data from included articles. The main results were summarised and analysed by Revman5.4.

Results

The meta-analysis included eight related RCTs involving 383 patients. All included studies were of moderate to high quality using the Cochrane Collaboration's tools for assessing the risk of bias.The results showed no significant improvement in Schirmer's test for the right [(RR 1.25, 95 % CI -0.68 to 3.18, heterogeneity I^2=97%),] left eye (RR 5.15, 95%CI-1.73 to 12.02, heterogeneity I^2=97%), right breakup time with fluorescein (RR 1.91, 95%CI -0.46 to 4.27, heterogeneity I^2=89%) and left breakup time with fluorescein (RR 1.74, 95%CI -0.29 to 3.77, heterogeneity I^2=87%) between ss and control groups. However, significant improvements were observed in the whole saliva test [(RR 0.20, 95%CI 0.09 to 0.30, heterogeneity I^2=90%)], and Bijsterveld's score for both left (RR -4.18, 95%CI -7.14 to -1.21, I^2=90%) and right eyes (RR -4.11, 95%CI -7.37 to -0.85, I^2=92%), as well as in fluorescein 1% staining for the left (RR -0.81, 95%CI -1.26 to -0.36, I^2=0%) and right eyes (RR -0.74, 95%CI -1.19 to -0.28, I^2=0%).

Conclusion

Based on the current evidence, oral pilocarpine does not significantly improve Schirmer's test results or breakup time with fluorescein BUT in patients with SS. However, it does enhance outcomes in the whole saliva test, Bijsterveld's score, and fluorescein 1% staining. These findings support the partial efficacy of pilocarpine in treating SS, with notable improvements in specific diagnostic measures. Further research is needed to fully understand the benefits of pilocarpine.

Key words

pilocarpine, Sjögren's syndrome, randomised controlled trials, curative effect

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Introduction

Sjögren's syndrome (SS) is a chronic autoimmune exocrine disorder characterised by lymphocyte infiltration that leads to anatomical and functional changes in exocrine glands, primarily affecting the salivary and lacrimal glands. This infiltration reduces glandular secretion, resulting in symptoms such as dry eyes and dry mouth. The condition is categorised as either primary or secondary, with the latter occurring as a complication of another connective tissue disease, such as rheumatoid arthritis or systemic lupus erythematosus. There is no recognised clinical difference between primary and secondary SS, and histopathological changes are the same. Therefore, the treatment objectives of SS include relief of dry symptoms, prevention of complications, and appropriate intervention of extra glandular manifestations. At present, different treatments have been proposed to alleviate patients' symptoms and change the course of the disease (1). However, systemic treatment in patients with SS has no beneficial effect on xerophthalmia (2). Therefore, the most common treatment for dry mouth and dry eyes is replacement therapy, including the use of local artificial lubricants as a substitute for naturally occurring tears. However, none of these preparations showed the same characteristics as the complex structure of natural lacrimal membrane (3).

Recent genetic studies have highlighted the involvement of Th-1 and Th-17 cells in the autoimmune response of SS (4-7), with the role of regulatory T cells still being explored (5). It is reported that the tear secretion of salivary and lacrimal glands is mediated by the M3 muscarinic acetylcholine receptor (M3R) (8, 9). Therefore, some studies have found that anti-M3R autoantibodies can inhibit saliva secretion (8). It has also been reported that anti-M3R antibodies may be involved in the pathogenesis of xerophthalmia in SS cases (10-12). Recently, oral pilocarpine, a cholinergic parasympathetic agonist, has been suggested to improve dryness in patients with SS.

Pilocarpine hydrochloride, a plant alkaloid and M3R agonist is derived from the leaves of the hairy fruit rue and lobular hairy fruit rue in South America (12). It stimulates salivary gland function through the muscarine M3 receptor and the parasympathetic nervous system when taken orally (13). It is reported that oral pilocarpine can increase saliva flow in patients with SS (8, 14). Initially, it was used to treat dry mouth caused by radiation and xerophthalmia in patients with SS. Recently, oral pilocarpine has been shown to effectively improve the symptoms and signs of dry mouth and dry eyes in SS patients (15, 16). The research varied in dosage (3 mg and 5 mg), timing of administration (during or after radiotherapy), and application method (swallowing, dissolving tablets in the mouth, or rinsing) (15). However, findings indicate that topical treatment is more effective than systemic administration (17). Other studies indicate that Sjögren's syndrome patients treated with pilocarpine experience a higher incidence of adverse effects compared to untreated individuals (18). However, pilocarpine may cause side effects due to its broad activity on muscarinic receptors across various organ systems. These adverse effects include excessive sweating, increased urination, gastrointestinal discomfort, and dizziness (19, 20). This may explain why pilocarpine is unpopular in most of the study population.

Given the increasing focus of recent research on improving symptoms in SS patients, this study aims to review the latest scientific evidence to evaluate the efficacy of oral pilocarpine in treating SS.

Materials and methods

Search strategy

All documents for this study were sourced from Pubmed, Web of Science, Cochrane, and Embase (until of November 2023). "Pilocarpine," "xerostomia," "xerophthalmia," "Sicca Syndrome," and "Sjogren Syndrome" are key terms for finding relevant and qualified articles. To minimise the risk of omitting pertinent studies, references from selected articles were meticulously reviewed to verify the robustness and validity of the meta-analysis. At the same time, we only collect data

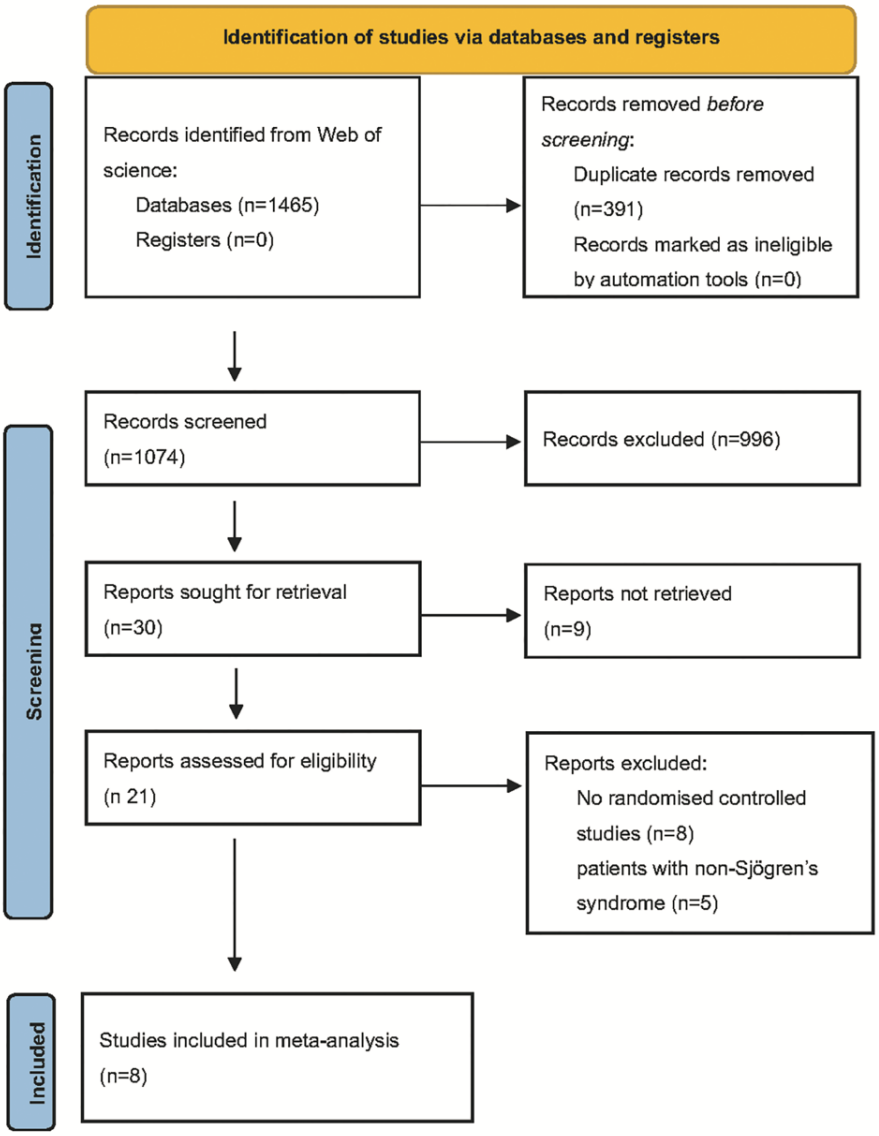

Fig. 1. Flowchart of selected articles.

from the full published papers, not including any conference abstracts.

Inclusion criteria and exclusion criteria

The inclusion criteria for studies in this meta-analysis are as follows: (a) randomised controlled trials (RCTs); (b) adult-based studies; (c) patients with SS must meet recognised diagnostic criteria; (d) if an article has been published more than once, we only use the latest version.

The criteria for the articles excluded from this meta-analysis were as follows: (a) reviews; (b) subjects are not human; (c) non-RCTs. Figure 1 shows a detailed flowchart of the inclusion and exclusion process.

Literature quality

The methodological quality of included RCTs was evaluated using the Cochrane Collaboration's tool for assessing risk in Review Manager 5.4. This tool delineates seven domains to measure potential biases (21): random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Each item was answered with one of the three replies: "low risk", "unclear risk", and "high risk" to assess the bias. Quality assessment was performed independently by two researchers, and if there was disagreement, they were discussed with other researchers.

Data extraction

Data extracted from each study included the first author's name, year of publication, number of patients participated in the study, original index, type of medication used, the dosage of the drug, method of measurement for the assessment of xerostomia, and outcomes for treatment and control groups.

Statistical analysis

Extracted data were subjected to statistical analysis using Review Manager software, version 5.4. Both the random effects model and the fixed effects model were used in this study. The fixed effects model posits that all studies derive from a common population, assuming no significant variation in effect size quantified either as odds ratios or standardised mean differences across studies. This assumption was tested using heterogeneity assessments, including the I^2 statistic and significance tests ($p<0.05$). An I^2 value greater than 50% or significant heterogeneity would invalidate the fixed effects model. The primary objective of this analysis was to assess the efficacy of pilocarpine in treating SS.

Results

Study characteristics

A total of 1465 articles were retrieved from Pubmed, Web of Science, Cochrane, and Embase, which were narrowed to 21 studies due to irrelevant titles and abstracts (Fig. 1). Further screening excluded five studies conducted on patients with non-Sjögren's syndrome and eight studies that utilised non-RCTs methods. Only eight studies that met our inclusion criteria were included in the meta-analysis, and all of them were RCTs. Finally, 383 SS patients were selected in this meta-analysis (Fig. 1). All eight studies were RCTs, and SS met the accepted diagnostic criteria. The basic characteristics of the articles required for this meta-analysis are shown in Table I and Table II.

Quality evaluation of included articles

The quality of the eight RCTs (22-29) included in the meta-analysis was rigorously assessed. The summary and

Table I. The basic characteristics of the included studies.

Study ID	Region (country)	Sample size (N/C)	Intervention	Control	Outcomes	Methods
N. L. Rhodus, DMD, MPH (1991)	(Minnesota) America	9/9	a pilocarpine-treated group	a control group	whole unstimulated saliva (WUS) and parotid stimulated saliva (PSS)	ophthalmic 2% pilocarpine solution, four drops three times a day (equivalent to 5 mg three times daily), to swish and swallow for 6 weeks
Frederick B. Vivino, MD (1999)	(Pennsylvania) America	127/125	2.5-mgpilocarpine, 5-mgpilocarpine	placebo tablets	In the global assessments of dry mouth and dry eyes at the study endpoint, specific symptoms associated with dry mouth and dry eyes were assessed, as was change in dryness associated with extraoral and extraocular symptoms, such as dryness of the skin, vagina, and nasal passages	drug with water 4times a day at mealtimes and bedtime, with a minimum of 3 hours between doses for the duration of the 12-week study
Athena S. Papas, DMD, PhD (2004)	(Boston) America	128/128	Pilocarpine-5mg	placebo	The primary endpoints were the patient's overall assessment of dry mouth and dry eyes. Changes in specific symptoms of dryness (mouth, eyes, nasal passages, skin, and vagina) were also examined	Take 1 tablet with water QID for 12 weeks. Their medication dose would be increased at 6 weeks, start at 5 mg
Cheng-Han Wu (2006)	(Taipei) Taiwan	23/21	pilocarpine	placebo tablets	The primary outcome of this study was the global improvement of dry mouth	four times daily (qid) at mealtimes and bedtime for 12 weeks
P Aragona (2006)	(Messina) Italy	15/15	pilocarpine hydro-chloride 5 mg tablets	studied before (T0)	Systemic and ocular symptoms, tear film break up time (BUT), corneal fluorescein vital staining, Schirmer I test, tear basal secretion test, and conjunctival imprinting was performed	For the first month, increasing doses from one to four tablets daily, increasing each week, were administered. In the second month, the therapeutic regimen of four tablets daily was followed, and the treatment was stopped at the end of the second month
N Tsifetaki (2015)	(Ioannina) Greece	29/28	oral pilocarpine (5 mg twice a day)	28 were assigned to be treated with artificial tears	The primary efficacy endpoint was the subjective assessment of a specific questionnaire using a series of VAS. A secondary efficacy endpoint was the objective measurement of tear flow using Schirmer's I test. An additional secondary efficacy endpoint was the objective measurement of the condition of the conjuctival epithelial cells using rose bengal and imprint tests.	5 mg twice a day, a period of 12 weeks
M. Cifuentes (2018)	(Santiago)Chile.	36/36	receive ten drops of pilocarpine (5 mg)	Ten drops of artificial saliva	salivary flow and lachrymal flow, their subjective global assessment, common side effects	orally, t.i.d.for 12 weeks
Sergio Felberg (2020)	(São Paulo) Brazil.	16/16	receive pilocarpine hydrochloride (5 mg)	placebo	The validated questionnaire NEI-VFQ 25 was applied to assess the impact of dry eye on the quality of life The dry eye-specific questionnaire Ocular Surface Disease Index (OSDI)	four times daily for a period of 10 weeks. After a 2-week washout period, a mandatory inversion of. the treatment was performed for an additional 10 weeks

graph of the risk of bias are shown in Figures 2 and 3.

The right eye Schirmer's test

Four RCTs reported the efficacy of pilocarpine in the Schirmer's test for the right eye in patients with SS. The heterogeneity test showed high heterogeneity (I^2= 97%, p<0.00001), so the random-effects model was used. The summary results showed that compared with the control group, The pilocarpine did not improve the treatment of SS of the right eye Schirmer's test (RR=1.25, 95%CI[-0.68, 3.18], p=0.22) (Fig. 4).

The left eye Schirmer's test

Four RCTs reported the left eye Schirmer's test. The heterogeneity test indicated substantial heterogeneity among the studies (I^2 = 97%, p<0.00001), necessitating the use of a random-effects model. The summary results revealed that compared with the control group, the pilocarpine did not improve outcomes in the treatment of SS as measured by left eye Schirmer's test (RR=5.15, 95%CI[-1.73, 12.02], p=0.14) (Fig. 5).

Table II. Extracted data of 8 studies in this meta-analysis.

Study ID	Participant	F/M (N/C)	Age (years) (N/C)	Height (cm) (N/C)	Weight (kg) (N/C)	Disease duration (years) (N/C)	Ethnicity (N/C)	Primary SS/ secondary SS
Rhodus (1991)	SS	(9/0)/ (9/0)	57.6±3.2/55.9±3.2	NA/NA	NA/NA	NA/NA	NA/NA	(3/6)/(3/6)
Vivino (1999)	primary or secondary SS	(124/3)/(118/7)	55.4±13.6/54.6±13.6	162.0±7.8/162.3±7.6	66.6±14.5/65.2±14.5	NA/NA	White 104, Black 3, Asian 14, Other 6/ White 97, Black 5, Asian 18, Other 5	NA/NA
Papas (2004)	SS	(117/11)/(125/3)	55.4±13.3/57.8±13.0	163.8±7.4/162.1±6.9	69.1±13.86/68.4±17.19	NA/NA	Caucasian 117, Black 7, East Asian 0, Other 4/Caucasian 116, Black 7, East Asian 1, Other 4	NA/NA
Wu (2006)	primary or secondary SS	(22/1)/(17/4)	57.1±11.9/56.4±12.5	157.3±4.5/159.9±5.5	53.1±8.2/55.7± 9.3	NA/NA	NA/NA	NA/NA
Aragona (2006)	primary SS	15/15	NA/NA	NA/NA	NA/NA	NA/NA	NA/NA	NA/NA
Tsifetaki (2015)	SS	(29/0)/(28/0)	57.0±11.5/59.9±9.9	NA/NA	NA/NA	10.5±6.1/10.5±5.4	NA/NA	NA/NA
Cifuentes (2018)	SS	(34/2)/(35/1)	52±11.15/53.17±11.66	NA/NA	NA/NA	22,16±16.24/23.28±15.31	NA/NA	(24/12)/(13/23)
Felberg (2020)	primary or secondary SS16/16		NA	NA	NA	NA	NA	NA

NA: not available; pSS: primary Sjögren's syndrome; SS: Sjögren's syndrome.

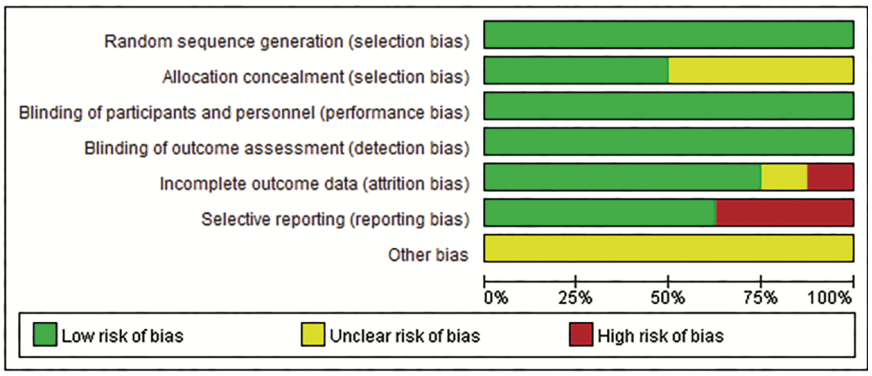

Fig. 2. The graph of risk of bias for the included RCTs.

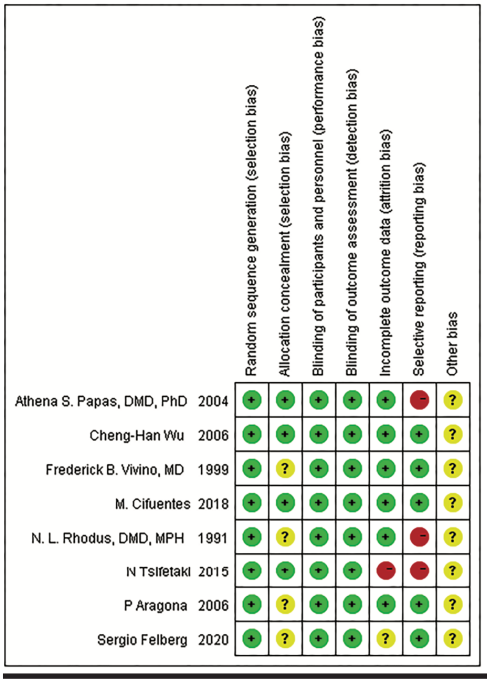

Fig. 3. The summary of risk of bias for the included RCTs.

The right eye breakup time with fluorescein

Two RCTs reported the right eye breakup time with fluorescein (BUT). The heterogeneity test showed significant heterogeneity ($I^2 = 89\%$, p=0.003), necessitating the use of a random-effects model. The summary results showed that compared with the control group, the pilocarpine did not improve the treatment of SS of right breakup time with fluorescein (RR=1.91, 95%CI[-0.46, 4.27], p=0.11) (Fig. 6).

The left eye breakup time with fluorescein

Two RCTs reported the left eye breakup time (BUT) with fluorescein. The heterogeneity test revealed significant heterogeneity ($I^2 = 87\%$, p=0.005), necessitating the use of a random-effects model. The summary results showed that compared with the control group, the pilocarpine did not improve the treatment of SS of left breakup time with fluorescein (RR=1.74, 95%CI[-0.29, 3.77], p=0.09) (Fig. 7).

Whole saliva test

Four RCTs reported the whole saliva test (WST). The heterogeneity test revealed elevated heterogeneity ($I^2 = 82\%$, p=0.02), which necessitated the use of the random-effects model. The summary results showed that com-

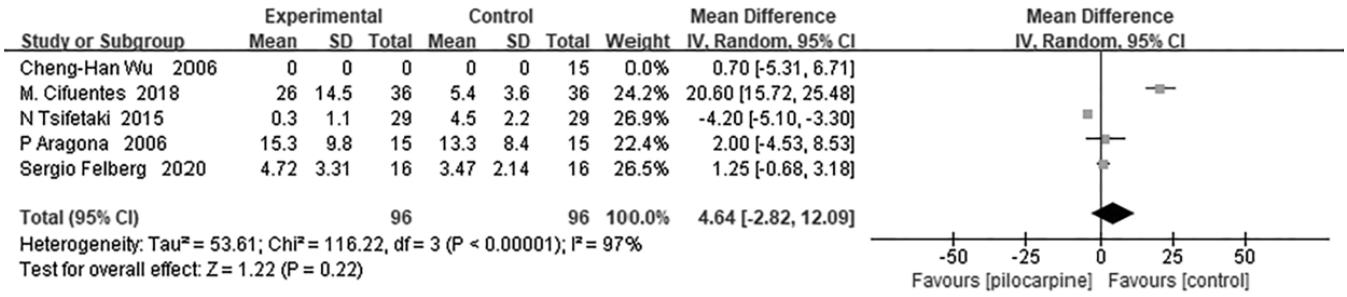

Fig. 4. Forest plot for the right eye Schirmer's test.
RR: relative risk; CI: confidence interval.

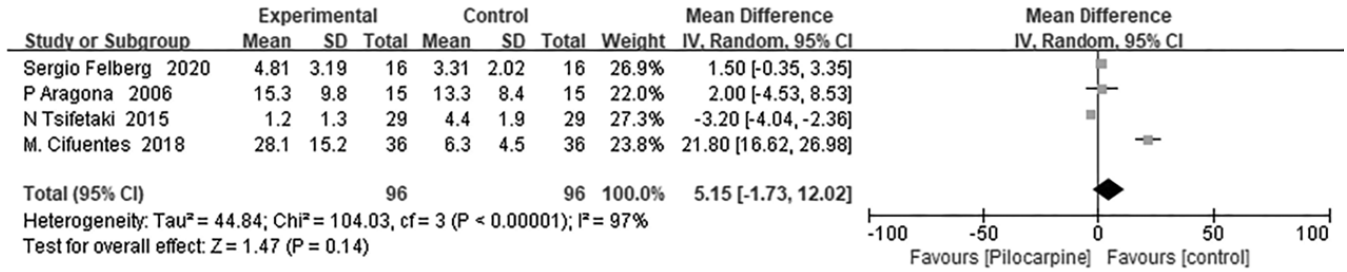

Fig. 5. Forest plot for the left eye Schirmer's test.
RR: relative risk; CI: confidence interval.

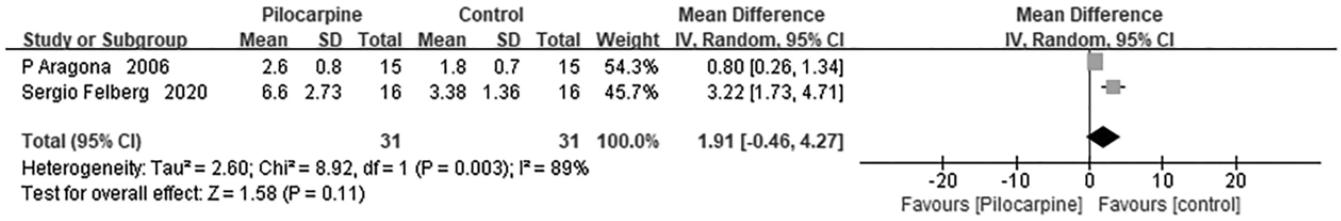

Fig. 6. Forest plot for the right eye breakup time with fluorescein BUT.
RR: relative risk; CI: confidence interval.

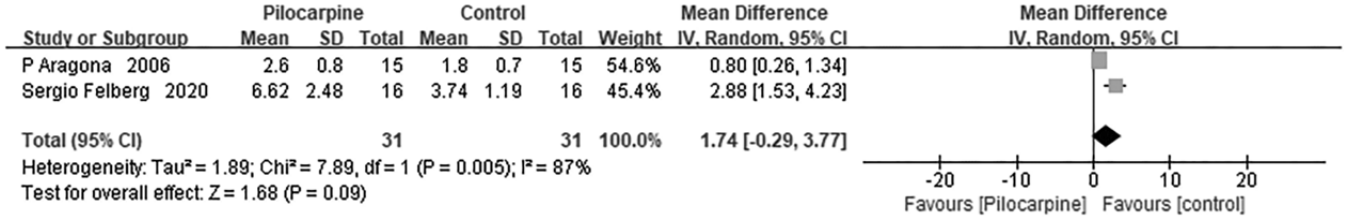

Fig. 7. Forest plot for the left eye breakup time with fluorescein BUT.
RR: relative risk; CI: confidence interval.

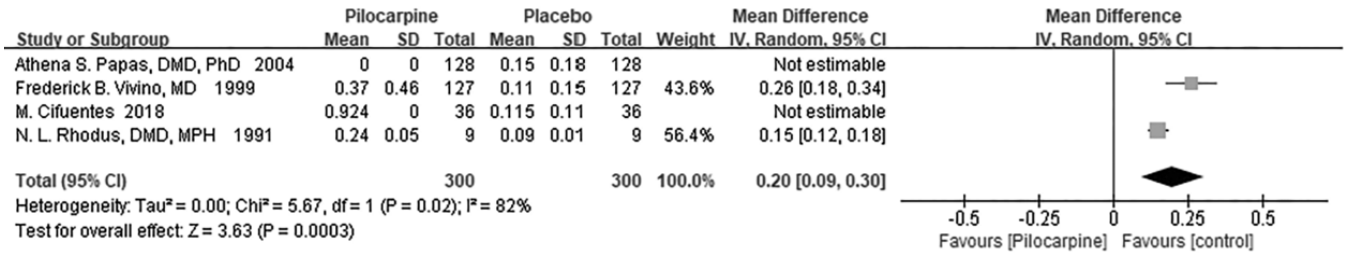

Fig. 8. Forest plot for the whole saliva test.
RR: relative risk; CI: confidence interval.

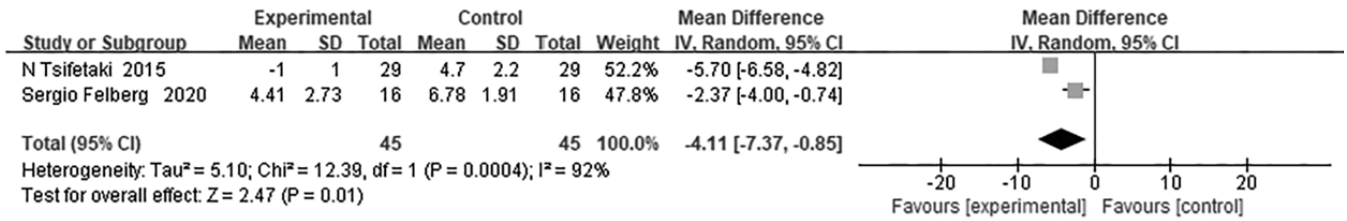

Fig. 9. Forest plot for the left Bijsterveld's score.
RR: relative risk; CI: confidence interval.

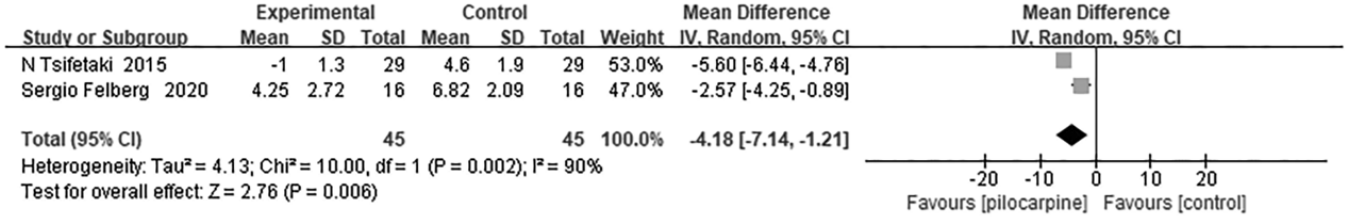

Fig. 10. Forest plot for the right Bijsterveld's score.
RR: relative risk; CI: confidence interval.

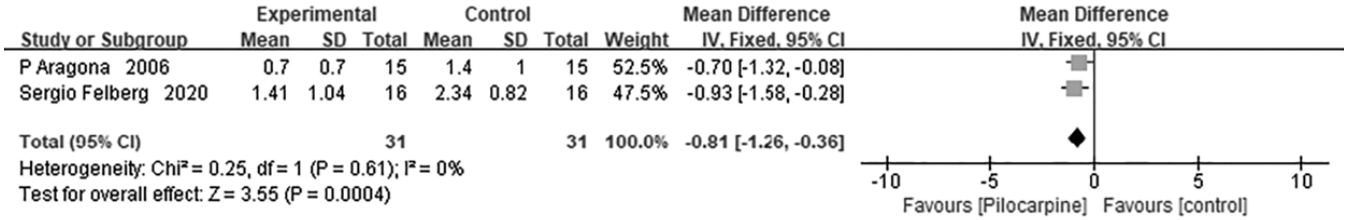

Fig. 11. Forest plot for the left fluorescein 1% staining.
RR: relative risk; CI: confidence interval.

pared with the control group, the pilocarpine did improve the treatment of SS of the whole saliva test (RR=0.20, 95%CI[0.09, 0.30], p=0.0003) (Fig. 8).

The left Bijsterveld's score

Two RCTs reported the left Bijsterveld's score. The heterogeneity test showed high heterogeneity (I^2 = 92%, p=0.0004), so the random-effects model was used. The summary results showed that compared with the control group, the pilocarpine did improve the treatment of SS of the left Bijsterveld's score (RR=-4.11, 95%CI[-7.37, -0.85], p=0.01) (Fig. 9).

The right Bijsterveld's score

Two RCTs reported the right Bijsterveld's score. The heterogeneity test showed high heterogeneity (I^2 = 90%, p=0.002), so the random-effects model was used. The summary results showed that compared with control group, The pilocarpine did improve the treatment of SS of the right Bijsterveld's score (RR=-4.18, 95%CI [-7.14, -1.21], p=0.006) (Fig. 10).

The left fluorescein 1% staining

Two RCTs reported the left fluorescein 1% staining. The heterogeneity test showed low heterogeneity (I^2 = 0%, p=0.61), which supported the use of a fixed-effects model. The summary results showed that compared with control group, the pilocarpine did improve the treatment of SS of the left fluorescein 1% staining (RR=-0.81, 95%CI[-1.26, -0.36], p=0.0004) (Fig. 11).

The right fluorescein 1% staining

Two RCTs reported the right fluorescein 1% staining. The heterogeneity test showed low heterogeneity (I^2 = 0%, p=0.86), which supported the use of a fixed-effects model. The summary results indicated a significant improvement with pilocarpine treatment for SS as assessed by right fluorescein 1% staining compared with the control (RR=-0.74, 95%CI[-1.19, -0.28], p=0.002) (Fig. 12).

Discussion

Our study thoroughly examined the study of pilocarpine in the treatment of SS, and given that it is a rare autoimmune disease with a scarcity of large-scale RCTs, our analysis included a considerable number of patients with this condition. In addition, this study constitutes the first RCT meta-analysis, which integrates all available evidence and investigates the possible impact of baseline differences on aggregate estimates. Through meta-regression analysis, we conducted this study to review the latest scientific evidence available to evaluate the efficacy of systemic pilocarpine in the treatment of SS.

The results of our meta-analysis showed that pilocarpine significantly improved WST, rose bengal test, and fluorescein staining in patients with SS compared

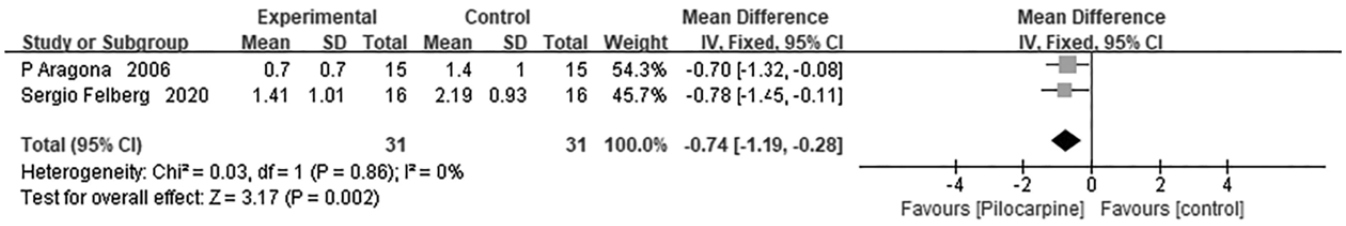

Fig. 12. Forest plot for the right fluorescein 1% staining.
RR: relative risk; CI: confidence interval.

with the control group. These significant improvements in saliva was consistent with previous studies (16, 30). However, our analysis also concludes that there was no improvement observed in the Schirmer's test and tear breakup time with fluorescein. Although the cause of this inconsistency is unclear, but maybe related to the frequency of pilocarpine use (twice, three, and four times a day) and dosage forms (tablets and drops).

No studies have reported serious side effects of pilocarpine in the treatment of SS that could be considered life-threatening. However, in these three studies (22, 23, 25), 16, 4, and 3 patients were reported to have opted out because of adverse reactions and lack of efficacy. These common adverse reactions include sialorrhea, sweating, headache, flu syndrome, nauseas, rhinitis, dizziness, bitter taste, diarrhoea, stomatodynia, sickness, sore throat, gastritis, dyspnea, urinary frequency, and herpes simplex. It is worth noting that all these symptoms are mild. However, previous studies (31) have shown a high incidence of adverse events, including sweating (43%), frequent urination (10%) and flushing (10%), which is also closely related to the mechanism of pilocarpine (32). However, alternative delivery methods, such as application to the oral mucosa or use in the form of soft lozenges, may minimise systemic exposure and local side effects, potentially reducing adverse reactions (33).

Several factors can influence the effectiveness of pilocarpine in treating SS; these include secretory reserve capacity of the affected salivary glands, the aetiology of xerostomia, age, contact area of oral mucosa, frequency of use, mode of administration, duration of administration, dosage forms, saliva collection methods, patient cooperation, the existence of patients' drugs and systemic diseases, and so on. This study also presents several limitations. Notably, not all SS patients included in this study are considered to have primary SS and may some may have secondary SS. Therefore, it is worthwhile to include only primary SS patients in future studies to evaluate the efficacy of oral pilocarpine in primary SS patients. Additionally, the impact of pilocarpine on oral mucosal absorption may vary significantly with each dose, which was not fully explored in this study that focused only on oral pilocarpine tablets without evaluating other forms of administration. The limitation of this study is that it only evaluates the oral use of pilocarpine tablets and does not comprehensively evaluate other uses of the drug.

Our meta-analysis also faced limitations. The absence of certain details in the original papers and the inability to contact the authors hindered a comprehensive evaluation of the data. There is a potential for publication bias, and the findings of our subanalyses were constrained by the small sizes of the studies included. Lastly, the overall sample size of our study was small, limiting the generalisability of the results.

Conclusion

Under the limitation of existing evidence, the efficacy of pilocarpine in the treatment of SS was evaluated. The results indicated no improvement in the eye Schirmer's test and the tear BUT with fluorescein, although there were improvements in the WST, Bijsterveld's score, and 1% fluorescein staining. However, at present, it is impossible to recommend the best dose and application. Therefore, in view of the limited number of studies included, it is necessary to further design well-designed multicentre and comparable schemes and follow-up time for RCTs.

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References

1. FOX RI, FOX CM: Sjögren syndrome: why do clinical trials fail? *Rheum Dis Clin North Am* 2016; 42(3): 519-530. https://doi.org/10.1016/j.rdc.2016.03.009
2. TSIFETAKI N, KITSOS G, PASCHIDES CA *et al*.: Oral pilocarpine for the treatment of ocular symptoms in patients with Sjögren's syndrome: a randomised 12 week controlled study. *Ann Rheum Dis* 2003; 62(12): 1204-7. https://doi.org/10.1136/ard.2002.003889
3. Management and therapy of dry eye disease: report of the Management and Therapy Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf* 2007; 5(2): 163-178. https://doi.org/10.1016/s1542-0124(12)70085-x
4. CRUZ-TAPIAS P, ROJAS-VILLARRAGA A, MAIER-MOORE S, ANAYA JM: HLA and Sjögren's syndrome susceptibility. A meta-analysis of worldwide studies. *Autoimmun Rev* 2012; 11(4): 281-7. https://doi.org/10.1016/j.autrev.2011.10.002
5. YAO Y, MA JF, CHANG C *et al*.: Immunobiology of T cells in Sjögren's syndrome. *Clin Rev Allergy Immunol* 2021; 60(1): 111-31. https://doi.org/10.1007/s12016-020-08793-7
6. YASUDA K, TAKEUCHI Y, HIROTA K: The pathogenicity of Th17 cells in autoimmune diseases. *Semin Immunopathol* 2019; 41(3): 283-97. https://doi.org/10.1007/s00281-019-00733-8
7. LONGHINO S, CHATZIS LG, Dal POZZOLO R *et al*.: Sjögren's syndrome: one year in review 2023. *Clin Exp Rheumatol* 2023; 41(12): 2343-56. https://doi.org/10.55563/clinexprheumatol/255qsx
8. FOX RI, STERN M, MICHELSON P: Update in Sjögren syndrome. *Curr Opin Rheumatol* 2000; 12(5): 391-8. https://doi.org/10.1097/00002281-200009000-00007
9. MAUDUIT P, JAMMES H, ROSSIGNOL B: M3 muscarinic acetylcholine receptor coupling to PLC in rat exorbital lacrimal acinar cells. *Am J Physiol* 1993; 264(6 Pt 1): C1550-C1560. https://doi.org/10.1152/ajpcell.1993.264.6.C1550
10. BACMAN S, BERRA A, STERIN-BORDA L, BORDA E: Muscarinic acetylcholine receptor antibodies as a new marker of dry eye Sjögren syndrome. *Invest Ophthalmol Vis Sci* 2001; 42(2): 321-7.

11. SUMIDA T, TSUBOI H, IIZUKA M, ASASHIMA H, MATSUMOTO I: Anti-M3 muscarinic acetylcholine receptor antibodies in patients with Sjögren's syndrome. *Mod Rheumatol* 2013; 23(5): 841-45. https://doi.org/10.1007/s10165-012-0788-5
12. KOMURO A, YOKOI N, SOTOZONO C, KINOSHITA S: Effectiveness of single-dose oral pilocarpine administration in patients with Sjögren's syndrome. *Diagnostics* (Basel) 2023; 14(1): 91. https://doi.org/10.3390/diagnostics14010091
13. PRONIN AN, WANG Q, SLEPAK VZ: Teaching an old drug new tricks: agonism, antagonism, and biased signaling of pilocarpine through M3 muscarinic acetylcholine receptor. *Mol Pharmacol* 2017; 92(5): 601-12. https://doi.org/10.1124/mol.117.109678
14. WU CH, HSIEH SC, LEE KL, LI KJ, LU MC, YU CL: Pilocarpine hydrochloride for the treatment of xerostomia in patients with Sjögren's syndrome in Taiwan--a double-blind, placebo-controlled trial. *J Formos Med Assoc* 2006; 105(10): 796-803. https://doi.org/10.1016/S0929-6646(09)60266-7
15. GIL-MONTOYA JA, SILVESTRE FJ, BARRIOS R, SILVESTRE-RANGIL J: Treatment of xerostomia and hyposalivation in the elderly: a systematic review. *Med Oral Patol Oral Cir Bucal* 2016; 21(3): e355-e366. https://doi.org/10.4317/medoral.20969
16. RAMOS-CASALS M, BRITO-ZERÓN P, BOMBARDIERI S *et al*.: EULAR recommendations for the management of Sjögren's syndrome with topical and systemic therapies. *Ann Rheum Dis* 2020; 79(1): 3-18. https://doi.org/10.1136/annrheumdis-2019-216114
17. KIM JH, AHN HJ, CHOI JH, JUNG DW, KWON JS: Effect of 0.1% pilocarpine mouthwash on xerostomia: double-blind, randomised controlled trial. *J Oral Rehabil* 2014; 41(3): 226-35. https://doi.org/10.1111/joor.12127
18. ALHASSAN M, ALDARWESH A, ALESSA I, ALHIJJI R, ALDUHAYAN R, ALMUSTANYIR A: Visual resolution under photopic and mesopic conditions in patients with Sjögren's syndrome. *Int J Ophthalmol* 2023; 16(10): 1662-69. https://doi.org/10.18240/ijo.2023.10.16
19. DAVIES AN, THOMPSON J: Parasympathomimetic drugs for the treatment of salivary gland dysfunction due to radiotherapy. *Cochrane Database Syst Rev* 2015; 2015(10): CD003782. https://doi.org/10.1002/14651858.cd003782.pub3
20. PANARESE V, MOSHIRFAR M: Pilocarpine (Archived). *In*: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024.
21. HIGGINS JP, ALTMAN DG, GØTZSCHE PC *et al*.: The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343: d5928. https://doi.org/10.1136/bmj.d5928
22. VIVINO FB, AL-HASHIMI I, KHAN Z *et al*.: Pilocarpine tablets for the treatment of dry mouth and dry eye symptoms in patients with Sjögren syndrome: a randomized, placebo-controlled, fixed-dose, multicenter trial. P92-01 Study Group. *Arch Intern Med* 1999; 159(2): 174-81. https://doi.org/10.1001/archinte.159.2.174
23. PAPAS AS, SHERRER YS, CHARNEY M *et al*.: Successful treatment of dry mouth and dry eye symptoms in Sjögren's syndrome patients with oral pilocarpine: a randomized, placebo-controlled, dose-adjustment study. *J Clin Rheumatol* 2004; 10(4): 169-77. https://doi.org/10.1097/01.rhu.0000135553.08057.21
24. CIFUENTES M, DEL BARRIO-DÍAZ P, VERA-KELLET C: Pilocarpine and artificial saliva for the treatment of xerostomia and xerophthalmia in Sjögren syndrome: a double-blind randomized controlled trial. *Br J Dermatol* 2018; 179(5): 1056-61. https://doi.org/10.1111/bjd.16442
25. WU CH, HSIEH SC, LEE KL, LI KJ, LU MC, YU CL: Pilocarpine hydrochloride for the treatment of xerostomia in patients with Sjögren's syndrome in Taiwan--a double-blind, placebo-controlled trial. *J Formos Med Assoc* 2006; 105(10): 796-803. https://doi.org/10.1016/S0929-6646(09)60266-7
26. FELBERG S, DANTAS P, SATO EH: Oral pilocarpine for the treatment of dry eye in patients with Sjögren's syndrome. *Arq Bras Oftalmol* 2022; 85(3): 269-76. https://doi.org/10.5935/0004-2749.20220069
27. TSIFETAKI N, KITSOS G, PASCHIDES CA *et al*.: Oral pilocarpine for the treatment of ocular symptoms in patients with Sjögren's syndrome: a randomised 12 week controlled study. *Ann Rheum Dis* 2003; 62(12): 1204-7. https://doi.org/10.1136/ard.2002.003889
28. RHODUS NL, SCHUH MJ: Effects of pilocarpine on salivary flow in patients with Sjögren's syndrome. *Oral Surg Oral Med Oral Pathol* 1991; 72(5): 545-49. https://doi.org/10.1016/0030-4220(91)90491-t
29. ARAGONA P, DI PIETRO R, SPINELLA R, MOBRICI M: Conjunctival epithelium improvement after systemic pilocarpine in patients with Sjogren's syndrome. *Br J Ophthalmol* 2006; 90(2): 166-70. https://doi.org/10.1136/bjo.2005.078865
30. BRITO-ZERÓN P, RETAMOZO S, KOSTOV B *et al*.: Efficacy and safety of topical and systemic medications: a systematic literature review informing the EULAR recommendations for the management of Sjögren's syndrome. *RMD Open* 2019; 5(2): e001064. https://doi.org/10.1136/rmdopen-2019-001064
31. RAMOS-CASALS M, TZIOUFAS AG, STONE JH, SISÓ A, BOSCH X: Treatment of primary Sjögren syndrome: a systematic review. *JAMA* 2010; 304(4): 452-60. https://doi.org/10.1001/jama.2010.1014
32. NUSAIR S, RUBINOW A: The use of oral pilocarpine in xerostomia and Sjögren's syndrome. *Semin Arthritis Rheum* 1999; 28(6): 360-67. https://doi.org/10.1016/s0049-0172(99)80002-x
33. HAMLAR DD, SCHULLER DE, GAHBAUER RA *et al*.: Determination of the efficacy of topical oral pilocarpine for postirradiation xerostomia in patients with head and neck carcinoma. *Laryngoscope* 1996; 106(8): 972-76. https://doi.org/10.1097/00005537-199608000-00011