• Meta-Analysis •

Effect of pharmacological pupil changes on intraocular lens power calculation: a systematic review and Meta-analysis

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Abstract

● **AIM:** To investigate the effect of pharmacological pupil alterations on intraocular lens (IOL) power calculations.

● **METHODS:** A systematic review and Meta-analysis of studies published before December 2023 in the PubMed, Embase, and Cochrane library databases on the accuracy of pharmacological pupil changes on IOL power calculation was performed. The primary outcome was the results of IOL power calculations before and after the use of medications. Subgroup analyses were performed based on participants' basic characteristics, such as age, axial length (AL), and whether miosis or mydriasis were used as classification criteria for further analyses. Each eligible study was evaluated for potential risk of bias by the AHRQ assessment scale. The study was registered on PROSPERO (CRD 42024497535).

● **RESULTS:** A total of 3062 eyes from 21 studies were eligible. There was no significant difference in the IOL power calculation before and after pharmacological pupil changes using any of the Hoffer Q (WMD=0.055, 95%CI=-0.046-0.156; *P*=0.29), SRK/T (WMD=0.003, 95%CI=-0.073-0.080; *P*=0.93), Haigis (WMD=-0.030, 95%CI=-0.176-0.116; *P*=0.69), Holladay 2 (WMD=-0.042, 95%CI=-0.366-0.282; *P*=0.80), and Barrett Universal II (WMD=0.033, 95%CI=-0.061-0.127; *P*=0.49) formulas. On the measurement of parameters related to IOL power calculation, for either miosis or mydriasis AL (*P*=0.98 and 0.29, respectively), lens thickness (*P*=0.96 and 0.13, respectively), and mean keratometry (*P*=0.90 and 0.86, respectively) did not present significant differences, while anterior chamber depth (*P*=0.07 and <0.01, respectively) and white-to-white distance (*P*=0.01 and 0.04, respectively) changed significantly between the two measurements prior and posterior. At the same time, despite there being some participants with the difference between the before and after calculations greater than 0.5 diopter, there was no significant difference in the incidence rate between these formulas.

● **CONCLUSION:** There is no significant effect of pharmacological pupil changes on the IOL power calculation. It will considerably reduce the visit time burden for patients who require cataract surgery.

● **KEYWORDS:** ocular biometry; intraocular lens; power calculation; cataract; pharmacological pupil alterations

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INTRODUCTION

Improved surgical techniques, modernized biometrics, updated formulae for intraocular lens (IOL) power calculations, and increased IOL quality have transformed cataract surgery from just vision restoration surgery to refractive surgery[1-2]. The accuracy of refraction is one of the success evaluation criteria for cataract surgery. Preoperative biometry directly determines postoperative refractive status. Olsen[3] showed that inaccuracy in anterior chamber depth (ACD), axial length (AL), and keratometry (K) were respectively responsible for 42%, 36%, and 22% of the predicted refractive error after IOL implantation.

Pharmacological pupil dilation, as part of the ocular examination before cataract surgery, not only evaluates the actual degree of opacity of the lens but also helps to exclude vitreous and fundus pathologies to reduce the risk of postoperative complications[4-5].

Pilocarpine is a first-line drug for the treatment of primary angle-closure glaucoma (PACG). Because of its affordable price and effectiveness in PACG patients, pilocarpine is widely used in Asian countries[6]. Lens extraction was able to deepen the anterior chamber and widen the chamber angle[7],

as well as reduce the risk of recurrence of angle closure[8], and the EAGLE study recommended it as a first-line treatment option for PACG[9]. Additionally, the FDA has approved the use of low concentrations of pilocarpine for the treatment of presbyopia[10], which has a high overlap with the population undergoing cataract surgery.

A significant number of patients who will undergo cataract surgery have to use pupil dilation or restriction medication when performing the preoperative examination. Previous studies have shown that pharmacological pupil changes can affect the measurement of some ocular biological parameters, while these changes may result in altered IOL power calculations based on these parameters. There is no clear consensus on whether the use of pupil dilation or restriction medications can cause changes in IOL power calculations. Therefore, the present study will conduct a Meta-analysis on the effect of pharmacological pupil changes on IOL power calculation.

MATERIALS AND METHODS

Search Strategy Two researchers (Tan SY and Liu DF) independently searched PubMed, Embase, and Cochrane library databases from the time of construction to December 2023 to investigate the effect of pharmacological pupil changes on the accuracy of IOL power calculations. The keywords used in the search included: “miosis”, “constricted pupil”, “pilocarpine”, “mydriasis”, “pupil dilation”, “cycloplegia”, and “intraocular lens”, *etc*. There was no restriction on the language of the publications. The articles listed in the index were reviewed in detail by two researchers, and discrepancies were resolved by the third researcher. This Meta-analysis was prospectively registered on PROSPERO (CRD 42024497535).

Inclusion and Exclusion Criteria Literature that satisfied the following criteria were included in the analyses: 1) cohort or cross-sectional studies; 2) interventions were use of drugs to dilate or restrict pupils; 3) studies reported results of IOL power calculations before and after the intervention; and at least one of the following types of IOL power calculations formulas was used: Hoffer Q, SRK/T, Haigis, Holladay 2 and Barrett Universal II; 4) optical biometric instruments were used; 5) each sample size was ≥15. The exclusion criteria were as follows: 1) inconsistent types of research, such as reviews and case reports; 2) unavailable data format for the results; 3) lack of clear description of the measurement instruments used; 4) unavailable full text; 5) duplicated participants in different studies.

Data Extraction and Quality Assessment Data were extracted independently by two researchers and discrepancies were resolved by the third researcher. For each published literature we extracted the following information: first author, publication date, study design, age, number of subjects, measurement instrument, intervention, results of IOL power calculations before and after the intervention, and relevant biometric measurements. Data were extracted using standardized forms.

The Agency for Healthcare Research and Quality (AHRQ) was used to assess the quality of each of the included studies. The scale objectively evaluates a study through 11 categories, and each category was answered with yes, no, or unclear. When answered yes, it scores 1, and when answered no or unclear it scores 0. Frequently scores between 0 to 3, 4 to 7, and 8 to 11 were defined as low, moderate, and high quality, respectively. Two authors independently assessed the quality of these studies and disagreements were resolved through discussion.

Statistical Analysis R software (R Foundation for Statistical Computing, Vienna, Austria) was used to perform Meta-analysis of the final included literature. When outcome indicators were continuous variables, weighted mean difference (WMD) was used for analysis with a 95% confidence interval (95%CI). When comparing the percentage of eyes with error >0.5 D before and after, analyses were performed by using a random-effected model with Freeman-Tukey double arcsine transformation. The level of significance for all statistical analyses was set at $P<0.05$. Heterogeneity was tested using the following I^2 values: if $I^2<50\%$ there was low heterogeneity between the studies and the fixed-effects model was used; if $I^2\geq50\%$ there was high heterogeneity between the studies and the random-effects model was used. Subgroup and sensitivity analyses were then performed to identify sources of heterogeneity. Subgroup analyses were performed based on participants’ basic characteristics, such as age, AL, and whether miosis or mydriasis as classification criterion for further analyses. The results are depicted in the form of forest plot. Funnel plots were used to assess publication bias.

RESULTS

Search Results As shown in Figure 1, a total of 2390 records were retrieved through the initial literature search, of which 670 were from PubMed, 1349 from Embase, and 371 from the Cochrane Library. After excluding 772 duplicates, and then excluding those that obviously did not meet the inclusion criteria by reading the abstracts, the remaining 42 documents were finally read in full. Ten studies did not report the results of interest, 4 did not use optical biometry, 5 with unavailable data forms, 1 with duplicate participants, and 1 with unavailable full text, which were excluded. Finally, 21 studies were included in the Meta-analysis.

Characteristics of Included Studies A total of 3062 eyes were involved in the 21 included studies. Of these 21 studies, 2 compared the results of IOL power calculations before and after pupil restriction with pilocarpine, and the remaining 19 reported the results from the use of dilating medication.

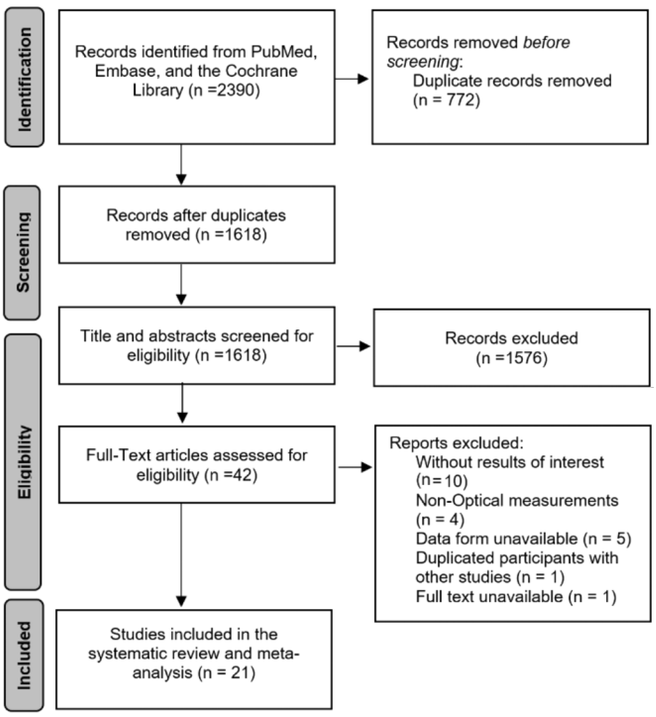

Figure 1 Flow chart of study selection.

These included studies involved at least one of the following 5 formulas: Hoffer Q, SRK/T, Haigis, Holladay 2, or Barrett Universal II. Table 1 showed the basic characteristics of the included studies[4-5,11-29].

IOL Power Calculations Figure 2 presented the results of the Meta-analysis of pharmacological pupil changes on IOL power calculations. Due to the low heterogeneity between studies (I^2=0, P=1.00), a fixed effects model analysis was used. Results showed that there was no significant difference in the IOL power calculation before and after pharmacological pupil changes using any of the Hoffer Q (WMD=0.055, 95%CI=-0.046–0.156, P=0.29), SRK/T (WMD=0.003, 95%CI=-0.073–0.080, P=0.93), Haigis (WMD=-0.030, 95%CI=-0.176–0.116, P=0.69), Holladay 2 (WMD=-0.042, 95%CI=-0.366–0.282, P=0.80), and Barrett Universal II (WMD=0.033, 95%CI=-0.061–0.127, P=0.49) formulas.

In addition, the Meta-analysis results of the proportion of eyes with calculations of IOL power changing more than 0.5 D were shown in Figure 3. Due to the high degree of heterogeneity (I^2=89%, P<0.01), a random effects model was chosen. The results suggested that although there was no difference in the before and after IOL calculations, it was worth noting that 20% (95%CI=0.164–0.239) of the participants still had an error in the before and after calculations of more than 0.5 D. While there was no significant difference in the error rates between the 5 formulas (P=0.22).

Biometric Results We have conducted a Meta-analysis of variations in measurements of biological parameters related to IOL power calculation in pharmacological pupil changes. AL (WMD=-0.003, 95%CI=-0.191–0.185, P=0.98), ACD

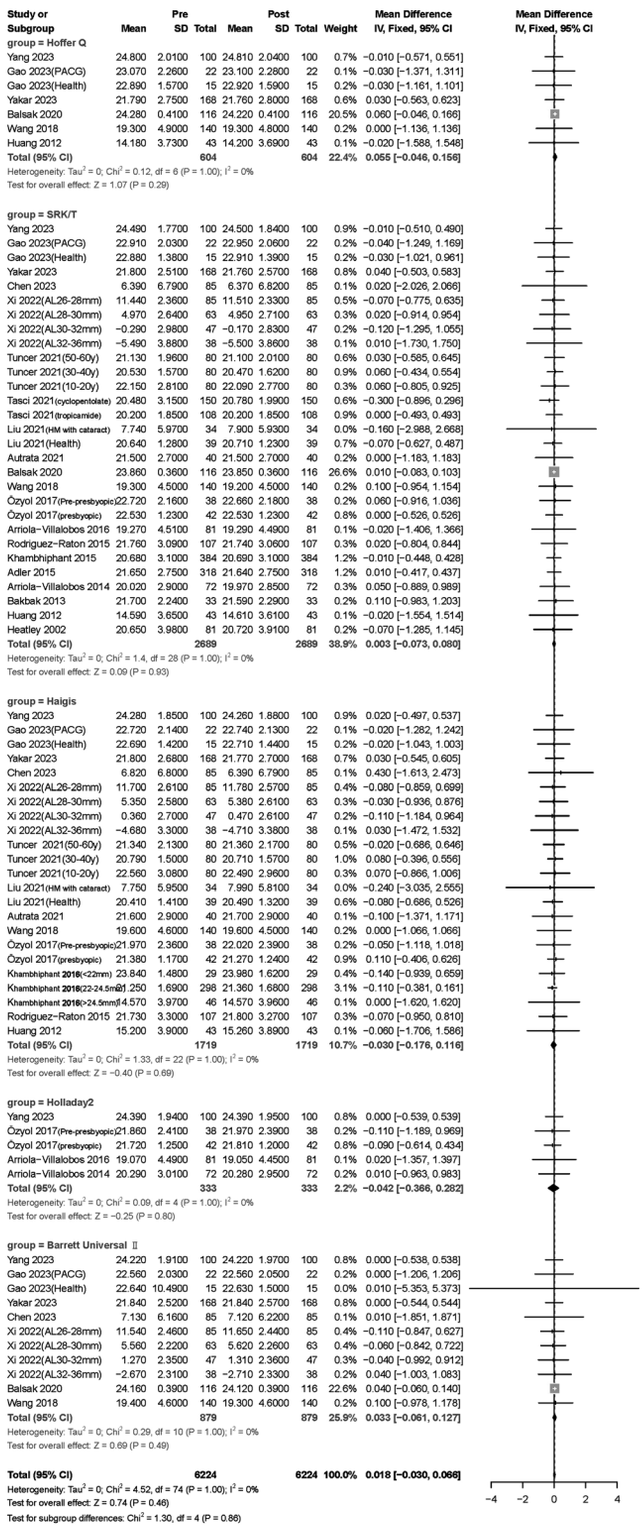

Figure 2 Forest plots for WMD of IOL power calculation before and after pharmacological pupil changes WMD: Weighted mean difference; IOL: Intraocular lens.

(WMD=0.054, 95%CI=-0.003–0.112, P=0.07), lens thickness (LT; WMD=-0.033, 95%CI=-0.114–0.047, P=0.42), and Km (WMD=0.026, 95%CI=-0.381–0.434, P=0.90) showed no significant differences in measurements before and after the use of pupil-restricting drugs, while white to white (WTW; WMD=0.080, 95%CI=0.017–0.43, P=0.01) measurements were significantly reduced. Measurements before and after

Table 1 Basic characteristics of included studies

Author, y	Study design	Participants	Age (y)	Number of eyes	Interventions	Measuring instruments	Formulas
Yang, 2023[11]	Prospective observational study	Primary angle closure disease	63.20±8.47	100	Miosis (pilocarpine)	IOLMaster 700	Hoffer Q, SRK/T, Haigis, Holladay 2, Barrett Universal II
Gao, 2023[12]	Observation study	Primary angle closure glaucoma/health	63.42±7.5/59.10±6.5	22/15	Miosis (pilocarpine)	Lenstar LS 900	Hoffer Q, SRK/T, Haigis, Barrett Universal II
Yakar, 2024[13]	Cross-sectional study	Health	59.22±11.57	168	Mydriasis (cyclopentolate)	Lenstar LS 900	Hoffer Q, SRK/T, Haigis, Barrett Universal II
Chen, 2023[14]	Observational study	High myopia	62.65±9.61	85	Mydriasis (tropicamide)	IOLMaster 700	SRK/T, Haigis, Barrett Universal II
Xi, 2022[5]	Prospective observational study	AL 26-28/28-30/30-32/32-36 mm	58.13±11.92	85/63/47/38	Mydriasis (tropicamide)	IOLMaster 700	SRK/T, Haigis, Barrett Universal II
Tuncer, 2021[15]	Cross-sectional study	50-60/30-40/10-20y	54.09±3.17/34.50±3.02/15.40±2.87	80/80/80	Mydriasis (cyclopentolate)	AL-Scan	SRK/T, Haigis
Tasci, 2021[16]	Observational study	Health	34.71±17.10	150	Mydriasis (cyclopentolate)	Lenstar LS 900	SRK/T
			30.67±16.90	108	Mydriasis (tropicamide)		
Liu, 2021[17]	Prospective observational study	High myopia with cataract/health	62.05±10.71/64.65±7.92	34/39	Mydriasis (tropicamide)	IOLmaster	SRK/T, Haigis
Autrata, 2021[4]	Observational study	Cataract	74.00±10.00	40	Mydriasis (tropicamide+phenylephrine)	Lenstar LS 900	SRK/T, Haigis
Balsak, 2020[18]	Prospective observational study	Children	8.40±0.32	116	Mydriasis (cyclopentolate)	Lenstar	Hoffer Q, SRK/T, Barrett Universal II
Wang, 2018[19]	Observational study	Children	10.00±2.00	140	Mydriasis (tropicamide+phenylephrine)	Lenstar LS 900	Hoffer Q, SRK/T, Haigis, Barrett Universal II
Özyol, 2017[20]	Cross-sectional study	Pre-presbyopic/presbyopic	30.10±6.80/56.60±7.30	38/42	Mydriasis (cyclopentolate)	IOLMaster 700	SRK/T, Haigis, Holladay 2
Khambhiphant, 2016[21]	Prospective observational study	AL<22.0/22.0-24.5/>24.5 mm	53.74±14.41	29/298/46	Mydriasis (tropicamide)	IOLMaster	Haigis
Arriola-Villalobos, 2016[22]	Observational study	Cataract	75.17±7.54	81	Mydriasis (tropicamide)	IOLMaster 700	SRK/T, Holladay 2
Rodriguez-Raton, 2015[23]	Prospective observational study	Cataract	74.65±7.27	107	Mydriasis (tropicamide+phenylephrine)	IOLMaster	SRK/T, Haigis
Khambhiphant, 2015[24]	Prospective observation study	Health	52.39±1.02	384	Mydriasis (tropicamide)	IOLMaster	SRK/T
Adler, 2015[25]	Prospective observational study	Cataract	71.93	318	Mydriasis (tropicamide+phenylephrine)	IOLMaster	SRK/T
Arriola-Villalobos, 2014[26]	Prospective observational study	Cataract	74.71±7.53	72	Mydriasis (tropicamide)	Lenstar LS 900	SRK/T, Holladay 2
Bakbak, 2013[27]	Cross-sectional study	Cataract	61.90±8.40	33	Mydriasis (tropicamide)	Lenstar LS 900	SRK/T
Huang, 2012[28]	Prospective observational study	Health	22.10±4.70	43	Mydriasis (tropicamide+phenylephrine)	IOLMaster	Hoffer Q, SRK/T, Haigis
Heatley, 2002[29]	Prospective observational study	Cataract	74.40±9.20	81	Mydriasis (tropicamide+phenylephrine)	IOLMaster	SRK/T

AL: Axial length.

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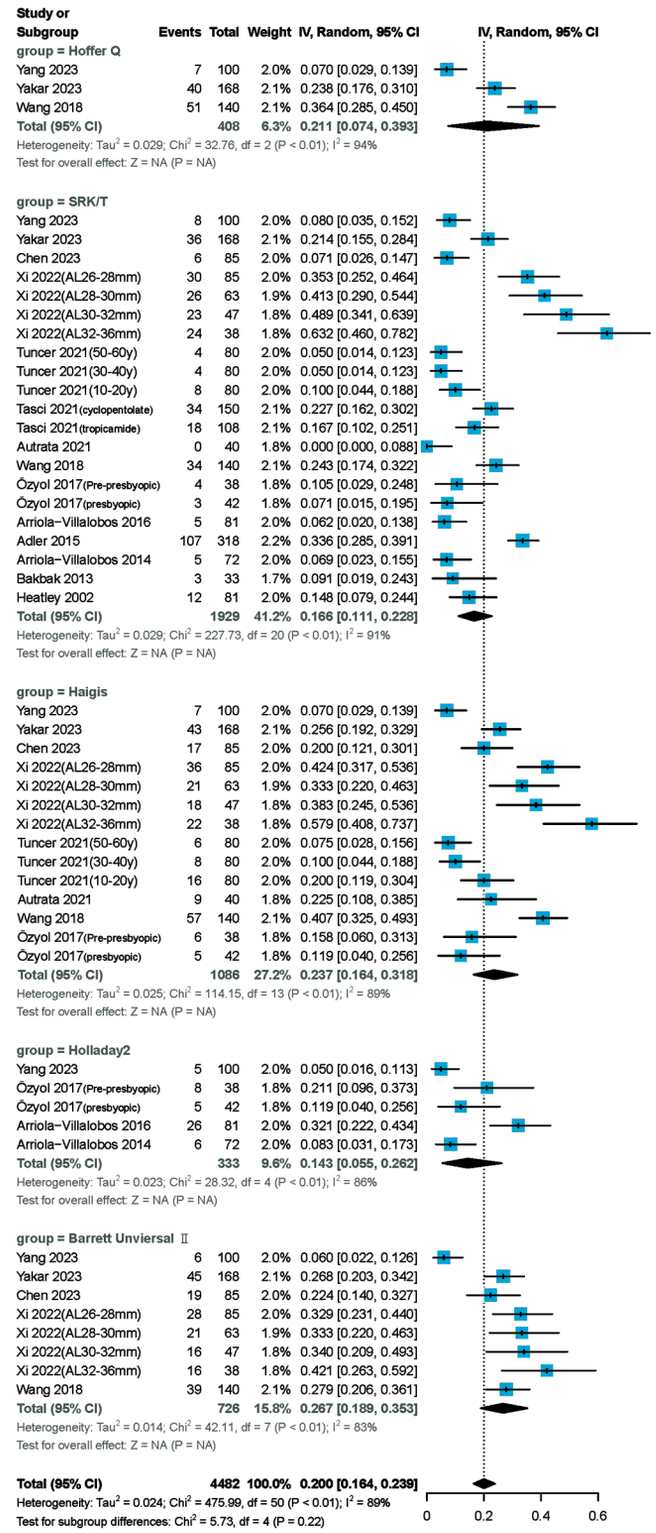

Figure 3 Forest plots for IOL power calculation error more than 0.5 D before and after pharmacological pupil changes IOL: Intraocular lens.

the use of pupil-dilating drugs showed no significant changes in AL (WMD=-0.013, 95%CI=-0.036–0.011, *P*=0.29), LT (WMD=0.045, 95%CI=-0.014–0.105, *P*=0.13), and Km (WMD=-0.017, 95%CI=-0.158–0.24, *P*=0.86), while ACD (WMD=-0.095, 95%CI=-0.123–0.067, *P*<0.01) and WTW (WMD=-0.035, 95%CI=-0.068–-0.002, *P*=0.04) measurements were significantly larger.

Subgroup Analysis Subgroup analyses were performed based on the age and AL of the participants in these studies. They were divided into three groups according to age: <18 years old, 18 to 40 years old, and >40 years old. No significant differences were found in the IOL power calculation before and after pharmacological pupil changes in the age subgroups (WMD=0.049, 95%CI=-0.026–0.124, *P*=0.20; WMD=-0.018, 95%CI=-0.245–0.208, *P*=0.87; WMD=-0.024, 95%CI=-0.120–0.073, *P*=0.63, respectively). Meanwhile, the proportion of errors greater than 0.5 D in the age subgroups was respectively 26.2% (95%CI=0.180–0.353), 13.7% (95%CI=0.088–0.195), and 20.3% (95%CI=0.158–0.251). In the subgroup analyses of different AL, since only a single study involved participants with short AL (<22 mm), subgroup analyses were performed on normal AL (22-24.5 mm) and long AL (>24.5 mm). There was no significant difference in the IOL power calculation in the normal AL subgroup (WMD=0.021, 95%CI=-0.028–0.070, *P*=0.40), with an error greater than 0.5 D proportion of 14.9% (95%CI=0.115–0.186); similarly, in the long AL subgroup there was no significant difference in the IOL power calculation (WMD=-0.045, 95%CI=-0.297–0.207, *P*=0.73), with an error greater than 0.5 D proportion of 35.5% (95%CI=0.280–0.433).

Quality Identification of Included Studies We assessed the quality of the 21 included studies with the AHRQ. The results showed that all studies were of moderate quality.

Sensitivity Analysis The sensitivity of the findings was assessed by sequentially excluding individual studies. The results showed that after excluding different studies, the results were comparable, indicating that the results of this study are reliable.

Bias Assessment The funnel plots shown in Figure 4 were used to assess publication bias. Funnel plot of the IOL power calculations in pharmacological pupil changes showed that all points were central and symmetrical, indicating that there was no significant publication bias.

DISCUSSION

In the practice of modern cataract surgery, the accuracy and reproducibility of ocular biometry is directly related to the assessment of surgical indications and superior surgical outcomes[16]. According to the European Registry of Quality Outcomes for cataract and refractive surgery report, the mean average biometric prediction error was 0.42 D, and after cataract surgery 72.2% of patients had a prediction error within 0.5 D[30]. Biometry has become one of the most important steps in modern cataract surgery. This Meta-analysis evaluation provides the latest evidence on the effect of pharmacological pupil changes on IOL power calculation. The findings suggested that preoperative examination undertaken while using pupil-modulating medication does not significantly affect the accuracy of IOL power calculation.

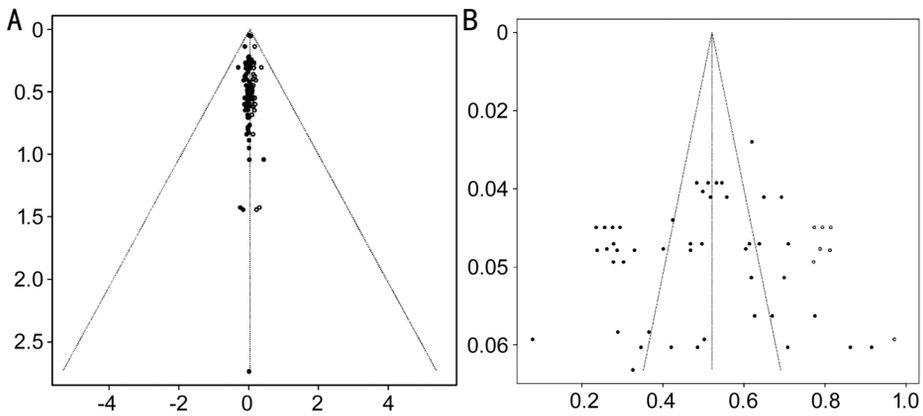

Figure 4 Funnel plots for WMD of IOL power calculation (A) and IOL power calculation error more than 0.5 D (B) before and after pharmacological pupil changes WMD: Weighted mean difference; IOL: Intraocular lens.

The new generation of calculation formulas not only takes into account more ocular biological parameters but also makes full use of advanced optical biometric instrumentation, to achieve a more accurate prediction of the effective lens position of IOL[31]. However, it is worth noting that the use of pupil-modulating medication is theorized to impact the measurement of ocular parameters, which in turn affects the accuracy of IOL power calculations. In this Meta-analysis, we found that medication can cause slight changes in ocular biometric parameters including ACD and WTW. However, these changes did not result in significant differences in IOL power calculation using the Hoffer Q, SRK/T, Haigis, Holladay 2, and Barrett Universal II formulas. Özyol *et al*[20] found that there was a mean difference of -0.11±0.21 D in the IOL power calculation with and without cycloplegia in pre-presbyopic eyes when using the Holladay 2 formulas (P=0.042). Xi *et al*[5] reported that there was a slight but significant difference of 0.112±0.348 D in the mean error of the Barrett Universal II formula for IOL power calculations before and after pupil dilation in the eyes with AL between 26 and 28 mm (P=0.004). The Holladay 2 formula incorporates seven variables, including AL, K, LT, WTW, ACD, preoperative refraction, and age of patients, to predict the effective lens position (ELP)[32]. As a representation of the 5-variable formula, the Barrett Universal II formula involves five biological parameters: AL, K, ACD, WTW, and LT[33]. The use of ACD improves the accuracy of IOL power calculations[34]. Previous studies have reported that each 1 mm deviation in corneal curvature diameter, AL, and ACD measurements resulted in 5.7, 2.7, and 1.5 D of refractive error, respectively[35]. Jeong *et al*[36] reported that preoperative ACD was the only significant factor affecting the prediction error of the IOL calculation formula. Similarly, Norrby *et al*[37] found that ACD could be used as the only parameter to accurately predict postoperative IOL position and when other parameters were included it did not improve the prediction accuracy. We found that ACD changed before and after the use of pupil-modulating medication in all included studies.

Another parameter that changed significantly before and after the use of pupil-modulating medication in this Meta-analysis was WTW. Previous studies have shown inconsistent results as to whether WTW changed significantly. Gao *et al*[12] did not find a significant change in WTW in PACG patients after the use of pilocarpine. In contrast, Yang *et al*[11] found that WTW changed significantly in primary angle closure suspect patients, which they proposed may be related to ciliary muscle contractility acting on the scleral spur and the peripheral cornea. In our analysis a slight but significant increase in WTW happened after pupil dilation. Tasci *et al*[16] and Wang *et al*[19] concluded that pupillary dilation does not affect WTW, whereas the research conducted by Chen *et al*[14] and Huang *et al*[28] achieved different results and they concluded that the change was related to the inaccuracy of measurement. The limbus is positioned by the border between the paler colored sclera the darker iris on the photographs taken by the machine. When the pupil dilates it makes this boundary more obvious, resulting in a change in location.

In practice, the power of IOL is usually adjusted in increments of 0.5 D. Our study statistics showed that pharmacological pupillary changes had a slight effect on IOL power calculations, but surgeons still need to be vigilant when performing IOL power measurement calculations in abnormal states. This is because the results of the current study suggested that pharmacological pupillary changes may indeed affect IOL power calculations by more than 0.5 D under certain circumstances. Compared with 20% of the overall population with an error greater than 0.5 D, in the <18 years old group this was 26.2% and in the long AL group this was 35.5%. Tuncer *et al*[15] found that there were significant increases in ACD in all groups after the use of cycloplegia, while the largest increase in ACD existed in the 10 to 20 years old group. Liu *et al*[17] observed that when using the Haigis formula, the percentage of errors greater than 1 D was 27% in the high myopia group

which was much higher than other groups. They concluded that this was related to the significant increase in ACD in the high myopia group after pupil dilation.

To the best of our knowledge, this was the first Meta-analysis based on the effect of pharmacological pupil changes on IOL power calculation. However, this article has the following limitations. 1) The analysis was based mainly on observational studies and the quality of the included studies was moderate. 2) There were fewer articles on the effect of pupil-restricting drugs on IOL power calculation, which resulted in limited statistical power. 3) We cannot completely exclude publication bias, although the funnel plot did not show signs of publication bias and the current results should be cautiously interpreted.

In conclusion, there was no significant effect of pharmacological pupil changes on IOL power calculation. That would significantly reduce the time burden of patient visits. At the same time, the proportion of larger errors is higher in younger and high myopia populations, and whether to use measurements calculated under unnatural conditions should be carefully considered.

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