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REVIEW/UPDATE

# Immediate sequential vs delayed sequential bilateral cataract surgery: systematic review and meta-analysis

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The main aim of this systematic review and meta-analysis was to evaluate the safety and efficacy profile of immediate sequential bilateral cataract surgery (ISBCS) compared with delayed sequential bilateral cataract surgery (DSBCS). MEDLINE Ovid, EMBASE, and CENTRAL databases were searched. Outcome measures were postoperative visual acuity, postoperative spherical equivalent (refractive outcome), endophthalmitis, corneal edema, pseudophakic macular edema, and posterior capsule rupture (PCR). 13 articles met criteria for final inclusion. A total of 11 068 622 participants (18 802 043 eyes) were included. No statistically significant differences between ISBCS and DSBCS were identified in all the postoperative outcomes evaluated. However, a higher risk for PCR was identified in the ISBCS group from the pooled analysis of non-randomized studies (risk ratio, 1.34, 95% CI, 1.08-1.67, $P = .0081$). In our view, the ISBCS approach has an acceptable safety-efficacy profile, comparable with DSBCS. Future investigations are warranted, with a focus on the analysis of risk factors for surgical complications, patient-reported outcome-measures, and cost effectiveness.

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According to the 2021 Global Burden of Disease Study, cataract is the leading cause of blindness worldwide and the second cause of vision impairment in adults aged 50 years and older.[1,2] Cataract extraction is one of the most performed surgical procedures worldwide.[1,2] The introduction of phacoemulsification, topical anesthesia, self-closing corneal incisions, foldable intraocular lenses (IOLs), and intracameral antibiotic administration has significantly ameliorated the safety–efficacy profile of cataract extraction. Cataract surgery achieves a high degree of optimal surgical outcomes with a fast rehabilitation period.[3]

Worldwide, the current standard of care is delayed sequential bilateral cataract surgery (DSBCS) in which patients with bilateral cataract have 2 separate operations usually scheduled 1 to 2 weeks apart. By contrast, immediate sequential bilateral cataract surgery (ISBCS) represents an alternative new approach in which both eyes are operated on in the same surgical session as 2 separate procedures.[4] In ISBCS, a complete aseptic separation of the first-eye and second-eye surgeries is required to minimize the risk of postoperative complications, with separate sets of surgical instruments, different batches of fluids, viscoelastics, and surgical instruments when disposable.

The safety profile, refractive accuracy, visual outcomes, and patient satisfaction of ISBCS vs DSBCS have been greatly debated in the past.[5] The fear of bilateral, sight-threatening sequelae of ISBCS (eg, endophthalmitis and postoperative macular edema) is the primary reason of concern for physicians and patients alike.[6] However, ISBCS allows faster visual recovery, shortened hospital stay and visits, with less time away from work, reduced travel time for surgery and postoperative follow-ups, and less dependence on others for supportive care.[7] In addition, adoption of ISBCS can lower healthcare costs because of the shorter turnover time between surgeries, avoidance of additional daycare admission, less use of home care, and reduction in travel costs.[4,8] Nonetheless, despite regional differences, same–surgical setting second-eye cataract surgery reimbursements rarely equalize the first-eye fees, a discouraging factor for providers.

Although some previous meta-analyses summarized the current data on the safety–efficacy profile of ISBCS, several prospective and retrospective studies have since been published, providing a more solid and conspicuous background

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for the analysis of the rare complications of cataract surgery.[9–14] In addition, a recent meta-analysis by Dickman et al. described a slight increased risk of complications associated with DSBCS.[11] The authors, however, did not examine each event individually but rather analyzed the combined proportions of intraoperative (eg, capsular rupture and hemorrhage) and postoperative complications (eg, corneal edema, retinal detachment, and cystoid macula edema).[11] Therefore, the results do not allow for any speculation regarding the actual cause of the disparity in increased risk between the 2 methods, nor do they suggest any specific measures that can be taken to mitigate this effect.[11]

The aim of this meta-analysis was to compare the visual and refractive outcomes as well as the complication rate of endophthalmitis, cystoid macular edema (CME), corneal edema, and posterior capsule rupture (PCR) of ISBCS compared with DSBCS.

## METHODS

This study was conducted in accordance with the principles in the Cochrane Handbook and reported in compliance with the PRISMA guidelines.[15] The study protocol was prospectively registered on the international prospective register of systematic reviews (PROSPERO) (ID: CRD42022360965). No deviations from the original protocol were recorded.

### Inclusion and Exclusion Criteria

The PICOS framework was used in developing the literature search strategy: patients (P)—male and female adults worldwide (>18 years old) with bilateral cataract; intervention (I)—ISBCS; comparator (C)—DSBCS; outcome (O)—corrected distance visual acuity (CDVA), postoperative spherical equivalent (SE), complication rate of endophthalmitis, persistent corneal edema, pseudophakic CME, and PCR or tear with and without vitreous loss; and study type (S)—prospective and retrospective studies.[16] Specifically, we included randomized controlled trials (RCTs) and excluded those with crossover or cluster-randomized design. In addition, both prospective and retrospective nonrandomized studies (NRSs) were included to account for the expected low incidence rates of some of the complications (eg, unilateral or bilateral endophthalmitis and PCR), despite the expected high risk of bias (RoB) invariably carried by these studies. The outcomes from the most recent publication for each study were included.

In our analysis, studies met inclusion criteria if the cataract extraction procedure was conducted through small incision phacoemulsification and IOL implantation. Notably, studies were excluded if (1) they were not reported in English; (2) the article type was a conference abstract, a review, a case report, a book chapter, or a letter to the editor; or (3) the cataract extraction procedure was not conducted through phacoemulsification.

### Outcome Measures

The aim of this systematic review and meta-analysis was to compare ISBCS and DSBCS regarding visual and refractive outcomes as well as intraoperative and postoperative complication rates. For a more conservative approach, we defined postoperative CDVA as the proportion of eyes achieving a final visual acuity of > 20/40. This outcome measure is based on our cohort of eyes presenting with ocular comorbidities, such as age-related macular degeneration (AMD), glaucoma, or diabetic retinopathy. Regarding refractive accuracy, we defined the postoperative SE as the proportion of eyes achieving an equivalent refraction within 0.50 diopter (D) from the intended target. The interval between the last performed surgical procedure and the nearest visual and refractive assessment did vary from 3 weeks to up to 1 year. This large timeframe was selected to account for the variability in the postoperative follow-up schedules and to optimize the completeness of postoperative data while providing time for vision to stabilize after surgery.[5,17–20] The earliest measurement of both CDVA and SE was preferred to minimize the late postoperative effects of ocular comorbidities and posterior capsular opacification.[17,21,22]

In terms of complications, the diagnosis of endophthalmitis was defined according to the definition provided in the Endophthalmitis Vitrectomy Study.[23] Persistent corneal edema was defined as the presence of a pseudophakic corneal edema and persistent endothelial cell damage within 30 days of surgery.[24] PCR and CME were defined according to the criteria specified in the National Ophthalmology Database audit.[25]

### Data Source and Study Search

An electronic search was performed on MEDLINE Ovid, EMBASE, and CENTRAL using relevant keywords, phrases, and medical subject heading terms. The search strings applied for different databases are reported in the supplementary material (Supplemental Data 1, available at http://links.lww.com/JRS/A910). The snowballing method was applied to the reference list of included articles to screen for additional RCTs and NRSs comparing ISBCS and DSBCS. The last search was performed on April 24, 2022. All data relevant to the study are included in the article or uploaded as online supplemental information. All the data included in our study are from published studies which can be searched in MEDLINE Ovid, EMBASE, and CENTRAL.

### Selection of Studies and Data Extraction

The reference lists from the 3 databases (MEDLINE Ovid, EMBASE, and CENTRAL) were merged, and duplicate entries were removed using the reference management software EndNote X9 (v. X9.3.3). After the screening of titles and abstracts independently conducted by 2 reviewers, the full texts of the remaining articles were analyzed. In the presence of eventual discrepancies in the selection process, a third reviewer was consulted.

The following variables were extracted from each included article: author and year of publication; type and setting of the study; country of origin; inclusion and exclusion criteria applied; recruitment period; length of follow-up; antibiotic prophylaxis, anesthetic, and anti-inflammatory strategy applied; time lag between the first and the second procedure in the DSBCS group; data source for retrospective studies; total number of screened subjects; number of male and female subjects in the ISBCS and DSBCS groups; total number of eyes in the ISBCS or DSBCS group; preoperative visual acuity; age at the time of surgery; presence of ocular comorbidities (eg, AMD, glaucoma, and diabetic retinopathy); number of eyes in the ISBCS/DSBCS group presenting a postoperative CDVA >20/40; number of eyes in the ISBCS or DSBCS group presenting a postoperative SE within 0.5 D from the intended refraction; and number of eyes diagnosed with postoperative endophthalmitis, CME, persistent corneal edema, and PCR in the ISBCS and DSBCS groups.[26]

Data extracted from selected articles by 2 reviewers working independently were archived in a customized Excel (Microsoft Corp.) spreadsheet with forced choice entry criteria. The data were registered as mean ± SD and number of participants/eyes for continuous variables and as number of events and number of participants/eyes for dichotomous variables. Whenever any relevant data were not available, we contacted the corresponding authors seeking additional information. However, no additional data were received. Hence, all data presented in this study derived from published sources. In the case of missing data, the corresponding study was excluded by the pooled analysis for that end point.

### RoB and Study Quality Assessment

Two reviewers independently assessed the RoB of the included articles. For RCTs, we applied the Cochrane's RoB-2 tool, rating each domain as low RoB, some concerns, or high RoB.[27] For NRSs,

we used the ROBINS-I tool, grading each domain as low RoB, moderate RoB, serious RoB, critical RoB, or no information on RoB.[28] Every disagreement was resolved by discussion.

### Data Synthesis and Statistical Analysis

All the analysis was performed using R software for statistical computing (R 1.4.1106; "meta" package). The unit of analysis (UoA) chosen for demographic factors was the number of subjects. Otherwise, the UoA was represented by the number of included eyes with a specified outcome. Data were pooled using a fixed or a random effects model according to the identified level of heterogeneity, following the recommendation of the Cochrane Handbook for Systematic Reviews of Interventions.[29] In the presence of <3 studies, a fixed effects model was chosen.[30] Pooled estimates from RCTs and NRSs were presented separately, as recommended by the Cochrane Handbook for Systematic Reviews of Interventions.[29] The mean difference was calculated as a measure of effect size to compare continuous variables, while the risk ratio was calculated for dichotomous variables. All results were expressed with 95% Clopper-Pearson CI. Statistical significance was defined as $P < .05$.

To assess heterogeneity among studies, we examined the forest plots of study outcomes to analyze the level of consistency considering the size and the direction of effects. In addition, we calculated the $I^2$ statistics to quantify heterogeneity, assuming values >50% as indicative of substantial heterogeneity.[30] The Cochrane $Q$ test was analyzed because the $I^2$ statistics underpowered in the presence of a low number of included studies. Specifically, we considered $P < .10$ to indicate statistical significance of the $Q$ test. The maximum-likelihood estimator was used to estimate the between-study variance ($\tau^2$). The risk of publication bias as quantitatively assessed by the Peters linear regression test was not performed nor was a funnel plot constructed because of the number of RCTs included being <10.[30,31] For the same reason, neither an influence, nor a subgroup or a sensitivity analysis was performed.[30,31] The assessment of the certainty of evidence per each outcome was independently performed by 2 authors using the GRADE framework and the GRADEpro GDT software (summary of findings 1 and 2, in the supplementary materials, available at http://links.lww.com/JRS/A894 and http://links.lww.com/JRS/A895).

## RESULTS

### Electronic Database Search Results and General Features of the Studies Included

A total of 2665 eligible articles were retrieved from the preliminary search on electronic databases. After the automatic removal of duplicates and the screening of both titles and abstracts, the full text of 102 articles was assessed for eligibility. Thirteen articles met criteria for final inclusion, all of which were published between 2006 and 2022 (Figure 1).[12–14,17,32–40] General features of the included studies are summarized in Supplemental Tables 1 and 2 (available at http://links.lww.com/JRS/A906 and http://links.lww.com/JRS/A907). Among them, 3 RCTs and 10 NRSs (both prospective and retrospective) were identified (Supplemental Tables 1 and 2, available at http://links.lww.com/JRS/A906 and http://links.lww.com/JRS/A907).[12–14,17,32–40] From 2002 to 2020, a total of 11 068 622 participants were included, of whom 311 967 (2.8%) underwent ISBCS compared with 10 756 655 (97.2%) who underwent DSBCS. The largest series was a multicenter retrospective cohort study that included 5 408 030 patients, while the smallest had 42 participants only.[14,33] Of the 13 eligible studies, 6 were conducted in the United States, 5 in Europe, 1 in Korea, and 1 in Iran.[12–14,17,32–40] The follow-up period was variable, with the longest being 12 months after the second-eye surgery. The timing and frequency of the antibiotic prophylaxis as well as the anesthetic strategy varied between studies (Supplemental Tables 3 and 4, available at http://links.lww.com/JRS/A908 and http://links.lww.com/JRS/A909). Similarly, some differences emerged in the time lag between the first and the second surgery in the DSBCS group (Supplemental Tables 1 and 2, available at http://links.lww.com/JRS/A906 and http://links.lww.com/JRS/A907). The included studies were conducted in private practices and both general and academic hospitals, with surgeries being conducted by both ophthalmic physicians and residents in training.[12–14,17,32–40] The analysis of demographic and clinical features of operated patients at baseline revealed a high level of heterogeneity for both RCTs and NRSs. Some statistically significant differences in the distribution of sex and comorbities emerged (Table 1). Overall, women seemed to be more represented than men in both study types. In addition, the AMD prevalence rate was higher in the DSBCS group compared with the ISBCS group, as reported in NRSs ($P = .0109$).

### RoB Assessment

As shown in Supplemental Tables 2 and 3 (available at http://links.lww.com/JRS/A908 and http://links.lww.com/JRS/A909), the RoB assessed with the RoB-2 and ROBINS-1 tools showed a generally moderate-to-low quality for both RCTs and NRSs. In both study types, the main limit derived from the nature of the intervention, which determined the unmasking of both investigators and recruited patients to the procedure applied.

In all but one included RCT, proper randomization protocols and concealment strategies were adopted.[36,37] However, only Sarikkola et al. provided information regarding the performed power calculation analysis.[37] Furthermore, only one of the included RCTs had a multicentric design.[36] Some concerns also emerged regarding the statistical methods and the data reporting strategies applied in the study by Lundström and colleagues, which was classified as being burdened by a high RoB.[40] In all but one RCT, deviations from the intended intervention might not be excluded because some patients in the ISBCS group had surgery on separate dates.[37,40] As this could result from technical issues or complications during the first-eye surgery and from not having the authors performed an analysis to estimate the effect of adhering to the intervention, a possible effect on the outcomes could not be excluded.

Among NRSs, 10 of 10 studies were rated as having serious RoB.[12–14,17,32–35,38,39] In fact, a high risk of confounding and immortal-time bias was evaluated. In addition, 4 of 10 NRSs were variably featured by unclear randomization protocols, inappropriate statistical methodologies, and inconsistent data handling and data reporting strategies.[33–35,38] In 6 of the included NRSs, data were obtained by clinical registries at a national level which generally use International Classification of Disease and Current Procedural Terminology codes.[12–14,17,32,34] In this context, the inclusion of misclassified or missing data should be considered. In addition, as per their retrospective nature, neither randomization nor prespecified periprocedural protocols were available for these studies.[12–14,17,32,34]

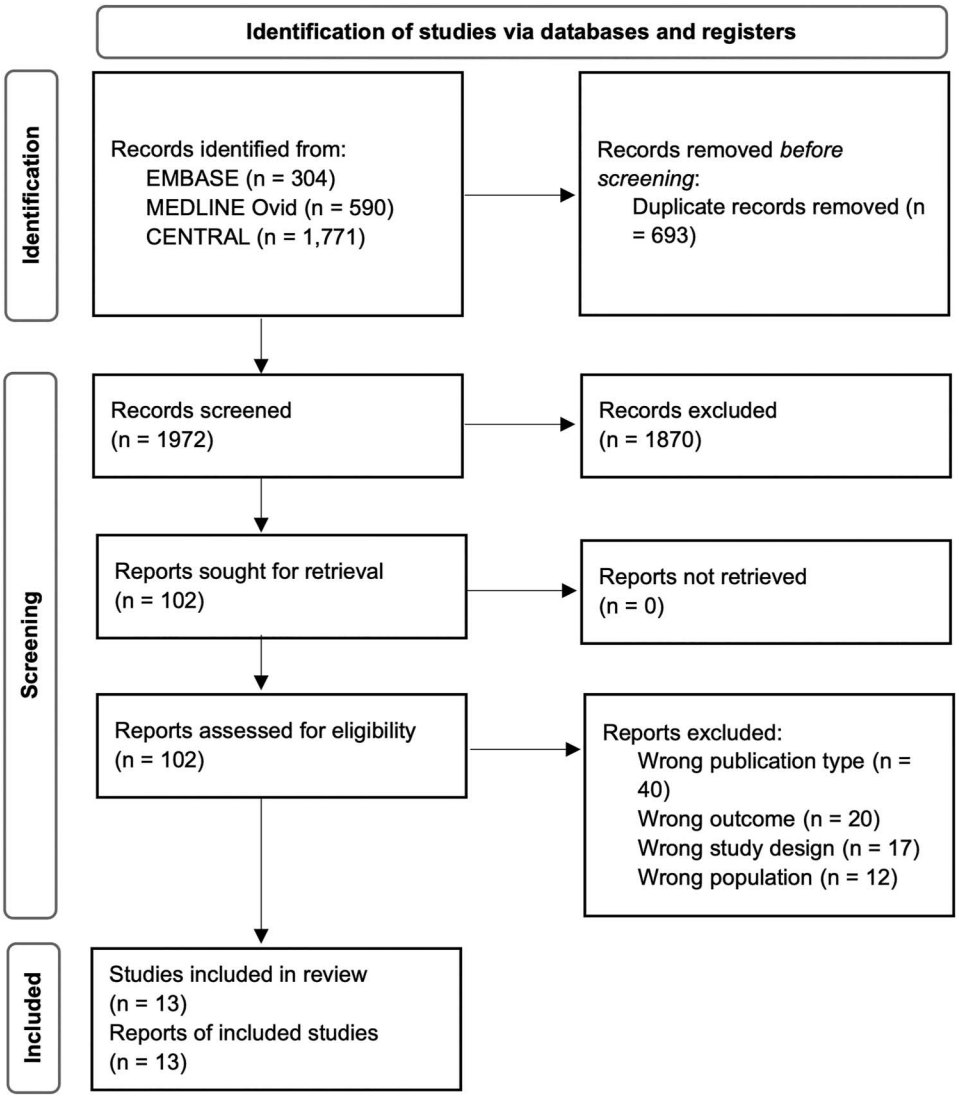



**Figure 1.** PRISMA flowchart. Reasons for exclusion are reported step-by-step on the right.

## Visual and Refractive Outcomes

In RCTs, 894 of 1191 eyes reached a postoperative CDVA >20/40 (75.1%, 95% CI, 72.5%-77.4%). Specifically, 468 of 593 eyes (78.9%, 95% CI, 75.5%-82.0%) that underwent ISBCS and 426 of 598 (71.2%, 95% CI, 67.5%-74.7%) eyes that underwent DSBCS had a postoperative CDVA better than 20/40 ($P = .0029$). Notwithstanding the statistically significant difference between the 2 groups, the low number of pooled studies (n = 2) along with the high heterogeneity of the analysis ($I^2 = 93.1\%$; $\tau^2 = 0.0186$; $Q$ test $P < .10$) indicate that negative intervention effects cannot be ruled out for future studies. For all comparisons, we used a fixed effects model because of the number of studies being <3 (Supplemental Figure 1, available at http://links.lww.com/JRS/A896).

When considering NRSs, 756 324 of 1 477 821 eyes presented a postoperative CDVA > 20/40 (87.9%, 95% CI, 36.5%-98.0%). Of those, 18 672 of 39 233 eyes (93.8%, 95% CI, 46.3%-99.6%) and 737 846 of 1 438 588 eyes (89.3%, 95% CI, 53.2%-98.4%) were detected in the ISBCS and DSBCS groups, respectively. No significant differences were identified for the number of eyes achieving a postoperative CDVA > 20/40 between the ISBCS and DSBCS groups ($P = .8959$). A random effects model was used for all comparisons because of the high level of heterogeneity (Supplemental Figure 2, available at http://links.lww.com/JRS/A897).

Overall, a moderate refractive accuracy was observed in the general ISBCS cohort, with 670 of 982 eyes (68.2%, 95% CI, 65.2%-71.1%) and 21 573 of 35 010 eyes (72.9%, 95% CI, 61.8%-81.6%) demonstrating a postoperative SE within 0.50 D from the predicted refraction in RCTs and NRSs, respectively. In RCTs, no differences were found in the refractive accuracy observed in eyes undergoing ISBCS compared with DSBCS ($P = .4973$). Although we found a higher percentage of eyes in NRSs with a postoperative refraction within 0.50 D from the target in the DSBCS group (75.5%; 95% CI, 61.9%-85.4%) compared with the ISBCS group (63.2%; 95% CI, 62.1%-64.3%), this difference was not statistically significant in our randomized effects model ($P = .5461$) (Supplemental Figure 3, available at http://links.lww.com/JRS/A898).

## Complication Rate

**Endophthalmitis Rate** No cases of endophthalmitis were recorded in the RCTs included in this meta-analysis (ISBCS

**Table 1.** Demographic and clinical features of the patients included in the meta-analysis at baseline

| Parameter | RCTs | | | NRSs | | |
|---|---|---|---|---|---|---|
| | ISBCS | DSBCS | *P* value | ISBCS | DSBCS | *P* value |
| Age (95% CI) | 72.1 (68.9, 75.2) | 73.5 (70.5, 76.5) | .1564 | 70.6 (67.5, 73.6) | 71.3 (67.5, 75.2) | .2756 |
| Sex (%) | | | | | | |
| Male (95% CI) | 35.5[a] (27.2, 44.8) | 35.3[b] (26.5, 42.3) | | 40.1[c] (39.2, 40.9) | 43.2[d] (38.3, 48.2) | |
| Female (95% CI) | 64.5[a] (55.2, 72.8) | 64.7[b] (54.8, 73.5) | | 59.8[c] (58.9, 60.7) | 62.6[d] (55.6, 69.1) | |
| Preop CDVA (logMAR) (95% CI) | 0.69 (−0.38, 1.77) | 0.69 (−0.33, 1.71) | .4424 | 0.59 (0.25, 0.93) | 0.52 (0.25, 0.79) | .2744 |
| Glaucoma (95% CI) | — | — | — | 11.8 (4.7, 26.3) | 13.9 (6.4, 27.8) | .0782 |
| AMD (%) | 25.8 | 19.9 | — | 10.1 (5.5, 17.6) | 13.2 (7.9, 21.3) | .0109* |
| DR (%) | 1.8 | 2.8 | — | 4.4 (2.2, 8.6) | 4.6 (2.8, 7.7) | .7722 |

AMD = age-related macular degeneration; DR = diabetic retinopathy; DSBCS = delayed sequential bilateral cataract surgery; ISBCS = immediate sequential bilateral cataract surgery; NRS = nonrandomized study; RCT = randomized controlled trial

*Statistically significant

[a].1540

[b].1615

[c]<.0001

[d].1611

n = 1127; DSBCS n = 1378). In the NRSs, we identified 5503 endophthalmitis cases of 7 281 012 (0.05%, 95% CI, 0.02%-0.09%) in both groups, of which 120 of 265 562 (0.04%, 95% CI, 0.01-0.11) were in the ISBCS group and 5383 of 7 015 360 (0.05%, 95% CI, 0.02%-0.10%) were in the DSBCS cohort. There was no evidence of an increased risk of endophthalmitis with ISBCS (*P* = .5876) (Supplemental Figure 4, available at http://links.lww.com/JRS/A899). Overall, 37 bilateral endophthalmitis cases of 7 281 012 (0.0003%, 95% CI, 0.0001%-0.0012%) were reported in both groups, at a rate of 1 of 265 652 (0.0004%, 95% CI, 0.0001%-0.0027%) among ISBCS eyes and 36 of 7 015 360 (0.0002%, 95% CI, 0.0000%-0.0016%) among DSBCS procedures. The UoA adopted for this outcome (ie, bilateral endophthalmitis) was the number of patients affected. No substantial differences existed between the 2 groups (*P* = .3838) (Supplemental Figure 5, available at http://links.lww.com/JRS/A900). Friling et al. reported the only case of bilateral endophthalmitis in the ISBCS group, involving a 93-year-old woman with poor general health and visually significant cataract in both eyes.[13] The patient underwent uneventful ISBCS, with prophylactic intracameral injection of cefuroxime 1 mg and ampicillin 100 mg. Six days after the surgery, the patient experienced decreased vision and pain in the right eye and was subsequently diagnosed with bilateral endophthalmitis caused by coagulase-negative staphylococci resistant to the perioperative prophylactic antibiotics but sensitive to vancomycin. Despite treatment, the patient's visual acuity remained compromised (20/125 in the right eye and counting fingers at 1 m in the left eye), and she died 1 month later because of worsening general health unrelated to the eye condition.

**CME Rate** In RCTs, 3 CME cases of 2805 were recorded, accounting for a rate of 0.11% (95% CI, 0.03%-0.33%). One of the CME cases was recorded in the ISBCS group (n = 1427; 0.07%, 95% CI, 0.01%-0.49%), while 2 were in the DSBCS cohort (n = 1378; 0.14%, 95% CI, 0.04%-0.58%), with no statistically significant differences between the 2 groups (*P* = .5855) (Supplemental Figure 6, available at http://links.lww.com/JRS/A901). A fixed effects model was chosen for all comparison being the heterogeneity level low.

In NRSs, 38 317 CME cases of 3 925 188 eyes were reported (0.91%, 95% CI, 0.39%-2.15%). Overall, the ratio of CME cases was 105 of 15 416 (0.75%, 95% CI, 0.36%-1.56%) and 38 212 of 3 909 772 (0.79%, 95% CI, 0.56%-1.13%) after ISBCS and DSBCS, respectively. In both cases, a randomized model was preferred, as per the high heterogeneity level ($I^2$ = 85 and 92%, respectively). No increased risk of CME was identified, according to our fixed effects model, in the ISBCS group compared with the DSBC one (*P* = .1255; $I^2$ = 17%) (Supplemental Figure 7, available at http://links.lww.com/JRS/A902). Interestingly, Chen et al. reported 2 cases of bilateral pseudophakic CME, with one patient undergoing ISBCS and the other DSBCS.[33] Despite the absence of surgical complications that could have contributed to the development of pseudophakic CME in the ISBCS patient, it should be noted that she had a history of diabetes without retinopathy. Both cases were successfully treated with topical nonsteroidal anti-inflammatory drops and steroids, resulting in a final CDVA of 20/20 in all eyes, according to the authors.[33]

**Corneal Edema Rate** In RCTs, 13 corneal edema cases of 1191 (1.09%, 95% CI, 0.63%-1.87%) were recorded by 2 studies that met the criteria.[37,40] Specifically, Sarikkola et al. described 7 corneal edema cases of 593 (1.18%, 95% CI, 0.56%-2.45%) and 6 cases of 598 (1.00%, 95% CI, 0.45%-2.21%) in the ISBCS and DSBCS cohorts, respectively (*P* = .7444) (Supplemental Figure 8, available at http://links.lww.com/JRS/A903).

Three NRSs only reported information regarding the corneal edema rate.[33,35,39] In this context, 1 corneal edema case of 340 eyes (0.29%, 95% CI, 0.04%-2.06%) was registered in a patient undergoing DSBCS (*P* = .9122) (Supplemental Figure 9, available at http://links.lww.com/JRS/A904).

For both NRSs and RCTs, a fixed effects model was preferred, being the number of NRSs < 3 and the heterogeneity level low in the context of RCTs.

No cases of bilateral corneal edema were reported by both RCTs and NRSs.

**PCR Rate** The PCR rate in this analysis was low in both the ISBCS and DSBCS groups. In RCTs, PCR was registered in

10 of 2613 cases (0.38%, 95% CI, 0.21%-0.71%), of which 4 of 1327 (0.30%, 95% CI, 0.11%-0.80%) and 6 of 1286 (0.47%, 95% CI, 0.21%-1.03%) were in the ISBCS and DSBCS groups, respectively. Lundstrom et al. did not specify the distribution of 2 PCR cases between the ISBCS and DSBCS groups.[40] According to our fixed effects model, there was no statistically significant difference in the risk for capsule rupture between the 2 groups ($P$ = .5454) (Supplemental Figure 10, available at http://links.lww.com/JRS/A905). In NRSs, 5985 PCRs of 624 446 (0.74%, 95% CI, 0.53%-1.02%) were recorded, of which 93 of 9722 (0.96%, 95% CI, 0.53%-1.73%) and 5892 of 524 724 (0.74%, 95% CI, 0.44%-1.22%) were in the ISBCS and DSBCS cohorts, respectively. Our fixed effects model, chosen for the low heterogeneity encountered ($I^2$ = 24%), identified a slightly increased risk of PCR in the ISBCS group (risk ratio, 1.34, 95% CI, 1.08-1.67, $P$ = .0078) (Figure 2).

## DISCUSSION

The main aim of this meta-analysis was to compare the surgical and visual outcomes of ISBCS and DSBCS. Thirteen studies were included, 3 RCTs and 10 NRSs, with sample sizes ranging from 78 to 7 722 098 eyes and post-intervention follow-up periods up to 12 months.

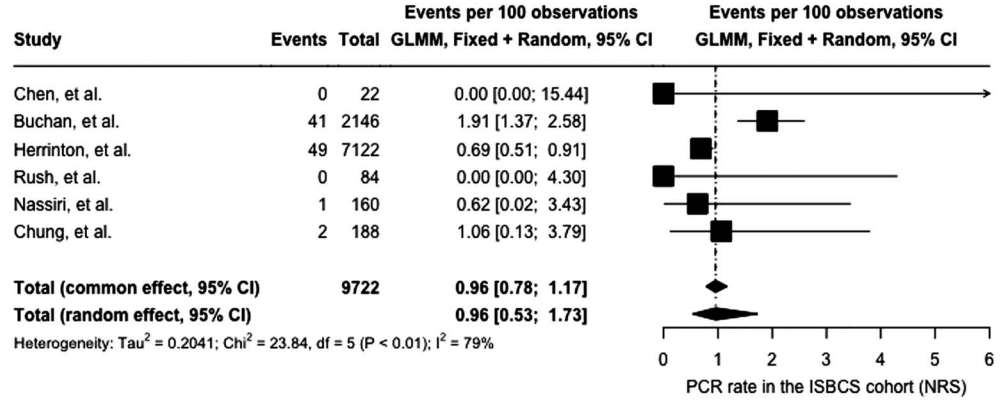
Overall, quantitative data on the safety and efficacy of ISBCS were limited. The certainty of evidence for all the prespecified outcomes was judged as low and very low, generally because of high RoB and imprecision.

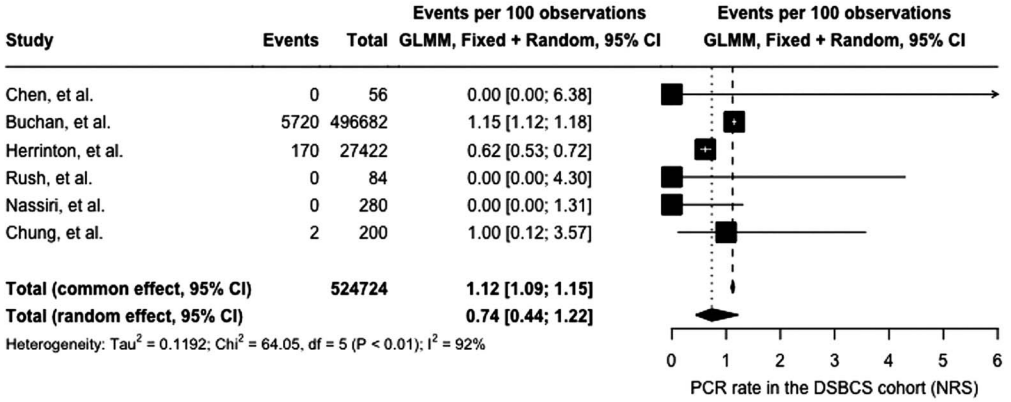
This meta-analysis found very low certainty evidence for no difference in visual outcomes between ISBCS-treated and DSBCS-treated eyes, based on data from 2 RCTs and 5 NRSs. From the analysis of data from 1 RCT and 3 NRSs, low and very low certainty evidence of no differences in the refractive accuracy of ISBCS compared with DSBCS was found. Specifically, nearly 75% of patients presented with postoperative emmetropia (defined as a postoperative SE within 0.50 D from the intended refraction), an estimate in line with the one of the 2019 annual reports of the European Registry of Quality Outcomes for Cataract and Refractive Surgery.[41] This evidence contravenes the assumption that DSBCS could be preferred because of the ability to refine the fellow-eye IOL power calculation based on the refractive outcomes of the first eye.[42,43] Several factors might explain this finding, including the introduction third and fourth generation IOL calculation formulas (Barrett Universal II, Kane, Olsen, etc.) or the usage of more reliable optical biometry.[44–46] One potential advantage of DSBCS still remains the ability to refine the calculation of IOL power in the fellow eye of a patient who has already undergone cataract surgery when an extended depth-of-focus (EDOF) lens is to be implanted.[45] Given the high variability in visual outcomes in the intermediate-to-near range associated with EDOF IOLs, the use of DSBCS may allow for better and more reliable results.[45] In addition, opting for mini-monovision with EDOF IOLS may necessitate the adoption of DSBCS to enhance the surgical planning for the fellow eye.[45]

By contrast, only a lower percentage of the eyes included in our cohort reached a final CDVA >20/40 (86.0 vs 96.0%). This difference is mainly based on the diverse way data from different included studies was reported. Some studies approached end points with more strict definitions of efficacy, such as percentage of eyes achieving 20/20 or 20/30, placing our figures as an underestimate.

Very low to low certainty level evidence of no increased risk of endophthalmitis was found in ISBCS when compared with DSBCS. For a long time, the main formal objection to the widespread adoption of ISBCS has been fear of the devastating risk of permanent blindness because of bilateral endophthalmitis or other complications (eg, bilateral CME, corneal failure, and toxic anterior segment syndrome [TASS]). Based on data coming from more than 15 million eyes, our analysis demonstrated that ISBCS poses a not dissimilar risk compared with DSBCS for the occurrence of either unilateral or bilateral endophthalmitis. Interestingly, no substantial differences either in the significance or in the direction of the effect emerged from the comparison of results from both RCTs and NRSs. Although no cases of endophthalmitis were reported by RCTs mainly because of the paucity of included patients, the descriptive and analytical information provided by NRSs seems reliable. In fact, the provided estimate is in line with the Swedish national study on the country's endophthalmitis rate of 0.029%.[47] When evaluating studies on this topic, it is critical to consider whether the sample size was sufficient to have observed any cases of endophthalmitis. Based on the power calculation analysis by Frilling et al., nearly 2 million eyes need to undergo ISBCS before any case of bilateral endophthalmitis would be reported.[13] Although our analysis included more than 15 million eyes between the 2 groups, only 533 444 cases were included in the ISBCS group, far below the provisional estimate. In addition, the same authors noted that the development of bilateral endophthalmitis is a serious concern that can lead to significant visual impairment in both eyes, resulting in a major impact on the affected individual's overall health status.[13] Furthermore, the societal and economic ramifications of such an event can be considerable.

Low to very low certainty evidence of no differences in the risk rate of other more common cataract surgery complications such as persistent corneal edema or pseudophakic CME was found. In addition, data from 3 RCTs demonstrated a very low certainty evidence of a similar risk of PCR in ISBCS-treated and DSBCS-treated eyes. However, low-grade evidence of an increased 1.3 risk of intraoperative PCR associated with ISBCS was reported according to 6 NRSs. Interestingly, the analysis for this outcome, pooling data of 534 446 eyes, presented a low level of heterogeneity ($I^2$ = 24%). Although we were unable to perform any metaregression analysis to assess the impact of eventual confounding factors (eg, AMD), the proposed results pave the way for several speculations.[48,49] First, it should be noted that the risk of PCR we observed in the ISBCS group was equal to the one reported for a consultant grade surgeon in the National Ophthalmology Database audit.[50] In addition, according to the National Institute for Health and Care Institute guidelines, ISBCS should be offered to "*people who need to have general anesthesia for cataract surgery but for whom general anesthesia carries an increased risk of complications or distress*" or to "*people who are at*



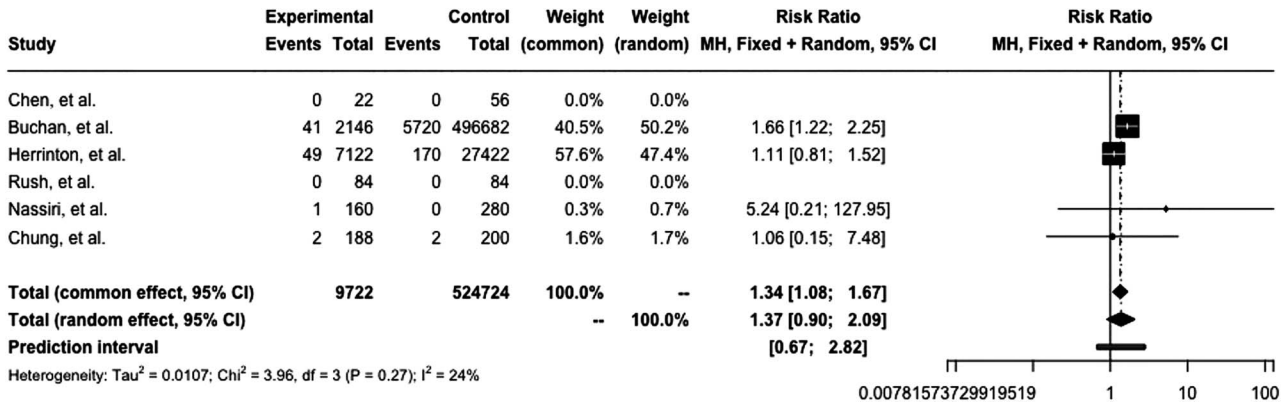




Figure 2. Forest plot showing the pooled percentage of eyes in the study and in the control group diagnosed with posterior capsule rupture and the risk ratio among them. Pooled data were obtained by nonrandomized studies only. DSBCS = delayed sequential bilateral cataract surgery; GLMM = generalized linear mixed model; ISBCS = immediate sequential bilateral cataract surgery; NRS = nonrandomized study; PCR = posterior capsule rupture

*low risk of ocular complications during and after surgery.*"[51] Although we did not analyze the eventual presence of systemic comorbidities, both the ISBCS and DSBCS cohorts seemed to present similar clinical and demographic features at baseline. Furthermore, a recent survey on the attitude of surgeons on the selection of patients to be proposed ISBCS demonstrated the "exclusion of high-risk eyes" as an important prerequisite for this approach.[52] Nonetheless, hypothesizing a homogenous distribution of complicated cases in the 2 arms, followed by the causes for the higher rate of PCR, should be attributed to non–patient-related factors, as follows.

In our opinion, the level of psychophysical stress experienced by the surgeon and the patient during ISBCS is the first element to consider. Accordingly, different sources of stress emerge in this context. In 2020, Lee et al. reported that specialist society approval and medicolegal/indemnity insurance approval represent the 2 most important factors that would allow for ISBCS to be considered by surgeons.[52] Similarly, in a large European-based survey, the respondents were asked to indicate the factor that would most influence their decision to consider ISBCS, with the most common circumstances reported as medicolegal and

indemnity insurance approval.[53] Undoubtedly, the lack of support from government and scientific bodies in endorsing ISBCS would expose surgeons to greater medicolegal issues in the event of any complications that arise during or after the surgery. Notably, in 2020, the Royal College of Ophthalmology and the UK and Ireland Society of Cataract and Refractive Surgeons presented a document recommending the adoption of ISBCS as a potential solution to the challenges posed by the COVID-19 pandemic.[54] A thorough evaluation of risks, a detailed analysis of the patient's suitability for the procedure, and the obtainment of their informed consent were deemed as essential prerequisites.[54] Clear guidelines for ISBCS have been established by the Royal College of Ophthalmology to minimize risks, as reported in Table 2.[54]

Furthermore, the extension of intraoperative procedural time elevates the risk for poor surgical outcomes.[55] In the context of cataract surgery, mainly performed under topical anesthesia, this deserves a critical appraisal. Laying still for prolonged periods of time or maintaining adequate fixation might become complex tasks for older patients or in the presence of systemic comorbidities (eg, cardiac heart failure and Pickwickian syndrome). In this setting, the surgeon and patient may experience higher levels of distress and/or discomfort, which may impair the proper course of the procedure.

This debate in ophthalmology is to continue, comparing the advantages of ISBCS against its drawbacks. Evidence and support for this approach have grown over time.[4] As a hint of progressing acceptance for ISBCS, both the American Academy of Ophthalmology and the National Institute for Health and Care Institute guidelines include specific discussion on ISBCS.[51,56]

The proponents of ISBCS claim that when specific guidelines are followed, the procedure is well-tolerated and as effective as DSBCS, with the added benefits of better short-term visual outcomes and faster rehabilitation time, avoiding intersurgery anisometropia and loss of stereopsis with DSBCS (Table 2).[9,10,42,54] In addition, the potential for ISBCS to yield higher productivity and cost savings seems not just intriguing but real.[43,54] Cost efficiency should further be taken into account when additional patient costs for travel and absence from work with the extra postoperative visits and recovery requirements of DSBCS are factored into the equation.[8] Finally, the most recent COVID-19 pandemic exposed the frailty of an already vulnerable medical system, constantly facing the effects of the "demographic time bomb" and of the constant lack of time-related, space-related, and personnel-related resources.[4,57–60] However, according to the data provided by the NRSs included in this study, the actual usage of ISBCS for bilateral cataract cases in real-world scenarios is only 3.4% (ISBCS n = 303 204; DSBCS n = 8 934 699), an estimate probably shaped by the combination of the extensive regulatory limitations and the doubts that surgeons hold toward ISBCS.

In a recently published meta-analysis on the topic, Dickman et al. investigated the visual and refractive outcomes and the global rate of surgical complications in ISBCS-treated and DSBCS-treated eyes. No differences between the 2 groups were reported.[11] Although these results do not significantly differ from ours, it is worth noting that the authors failed to analyze the odds for some of the most common surgical complications of cataract surgery (eg, PCR, CME, and corneal edema) in ISBCS and DSBCS eyes.[11] In addition, many recently published retrospective cohort studies were not included, and therefore, the results proposed by Dickman and colleagues are based on a significantly smaller sample size, an aspect which invariably affects the statistical power of the analysis. The authors did not observe any instances of bilateral endophthalmitis in the ISBCS group (37 cases analyzed in our study).[11] They also noted that the study of Herrinton et al. was the only one large enough to detect endophthalmitis as an event occurring unilaterally at least once in both the ISBCS and DSBCS groups (4 studies reporting at least 1 case of unilateral endophthalmitis in both groups in our study).[11,17] Nonetheless, the authors presented the proportion of complications as a combined metric, which hinders a proper understanding of the underlying causes of the events and precludes the implementation of any possible corrective measures.[11] In fact, the combined proportion of complications is not a clinically relevant measure because it fails to provide clinicians with the information necessary for proper patient counseling and effective surgical planning.

The findings of the recently published Bilateral Cataract surgery in the Netherlands study, a multicenter, noninferiority, randomized controlled clinical trial, corroborate our own data.[61] The authors concluded that ISBCS was noninferior to DSBCS in postoperative refractive outcomes within 1.0 D and 0.5 D of the desired refraction, as well as visual acuity outcomes.[61] Moreover, there were no significant differences in complication rates and patient-reported outcome measures between the 2 approaches. In addition, the authors estimated a potential yearly cost savings of $34.5 million, if ISBCS was chosen as the favored technique for bilateral cataract extraction.[61] In line with our review protocol (CRD42022360965), this study was excluded from the meta-analysis because we had already completed all the required steps of article screening, selection, and analysis before its publication.

Our meta-analysis is the first to take advantage of the data reported by the large retrospective studies conducted in recent years. The observational nature of the Intelligent Research in Sight Registry or the Swedish National Cataract Registry represents useful tools in providing sufficient statistical power for studying several medical conditions and their preferred treatment strategy, with an emphasis on clinical outcomes. Though extremely valuable, the analysis of retrospective studies undoubtedly carries a number of biases, including misclassification or nonreporting.[6] This is particularly applicable in the case of TASS.[62,63] From a descriptive point of view, 3 studies (describing 13 eyes) reported information on the presence of a sterile inflammatory process occurring in the anterior chamber of patients undergoing cataract surgery.[8,33,38] The most disparate definitions were used, including "persistent/recurrent AC inflammation," "anterior chamber flare," and "anterior uveitis." Although no

**Table 2.** Guidelines for Immediate Sequential Cataract Surgery developed by the Royal College of Ophthalmologist and the UK and Ireland Society of Cataract and Refractive Surgeons[a]

| Parameter | Absolute | Relative |
|---|---|---|
| Case selection | | |
| Inclusion criteria | Visually significant bilateral cataract with cataract surgery indicated for both eyes in adults<br>No absolute contraindications | |
| Exclusion criteria | Concomitant surgery for cornea, glaucoma, or retinal diseases<br>Previous significant eye surgery or significant eye injury, lens luxation, or phakodonesis<br>Increased risk of infection<br>Ocular comorbidity<br>Previous refractive surgery, especially if the patient still prefers spectacle independence<br>Concomitant glaucoma which is uncontrolled either eye<br>Iodine allergy | Extreme axial length (<21.5 mm or >26.0 mm)<br>Immune compromise or immunosuppression<br>Cooperation issues and increased risk of complications |
| Surgical consideration | Concomitant ocular and periocular disease should be controlled before surgery<br>Clear planning as to which eye to do first<br>Use of validated surgical safety operative checklist to avoid wrong intraocular lens and never events<br>Careful wound architecture and low threshold for suture use<br>Intracameral antibiotic at the end of the procedure<br>Any issue with the first-eye surgery must be solved before proceeding with the second-eye surgery<br>If there is a suggestion for a complication in the first eye, especially if it increases the risk for endophthalmitis or other adverse outcomes, second-eye surgery must be deferred | In the case of high refractive error, if expedite second-eye surgery cannot be performed, ISBCS may be considered for unilateral cataract, only if there are safety issues or if postoperative anisometropia cannot be managed in any other way<br>Topical anesthesia is preferred, with or without sedation, or subtenons in 1 eye only. Bilateral "block" should be avoided<br>It is important that, in training units, ISBCS do not reduce access to training opportunities |
| Complete aseptic preparation of the first-eye and second-eye surgery | Before the operation of the second eye, the surgeon and nurse shall use scrupulous sterile routines treating each eye as a completely separate procedure with a completely separate aseptic preparation<br>Theatre team to rescrub, regown, reglove, and undertake repeat prepping and draping of the surgical site<br>The separate instrument trays for the 2 eyes should go through complete and separate sterilization cycles with indicators<br>There should be no physical contact or cross-over of instruments, drugs, or devices between the 2 trays for the 2 eyes at any time before or during the surgery of either eye<br>Different batches/lots of surgical supplies should be used for each eye. This should be specified on ordering<br>Nothing should be changed regarding suppliers or devices used in surgery without a thorough review by the entire surgical team | Consider the use of disposable surgical instruments sets<br>Different IOL batches should be used for the 2 eyes |
| Counselling and consenting | The patient must be free to make an informed choice between ISBCS and DSBCS<br>The patient should understand the possible consequences of bilateral endophthalmitis, but also of other significant complications<br>Patients should be specifically advised that ISBCS loses the advantage of refractive adjustment for the second eye<br>For outlying axial lengths, additional tailored consent is required for risk (refractive surprises, additional complications) and benefit (stereopsis, neuroadaptation)<br>ISBCS is not suitable for 1-stop models in which preoperative assessment and consent are obtained on the day of surgery | |
| Other considerations | Both eyes of ISBCS patients should not be patched. One eye at least should have a clear shield<br>Patients should be able to instill postoperative eyedrops, or have arrangements for this to be performed by others<br>Results should be closely monitored and eventually compared with national standards | It is often helpful for patients to go home with a companion |

DSBCS = delayed sequential bilateral cataract surgery; ISBCS = immediate sequential bilateral cataract surgery

[a]Adapted from "The Royal College of Ophthalmologists Covid Response Team, UK and Ireland Society of Cataract and Refractive Surgeons. Immediate Sequential Bilateral Cataract Surgery (ISBCS) During COVID Recovery: RCOphth/UKISCRS Rapid Advice Document. London, UK: The Royal College of Ophthalmologists; 2020."

specific evidence for discrimination of TASS among them could be found, TASS could also be significantly underreported.

In addition, it is worth noting that out of all the articles included, only 1 specifically examined the clinical and surgical outcomes of ISBCS vs DSBCS performed by trainees.[33] As a result, conducting a separate analysis solely on this aspect was considered not clinically relevant. However, when examining the forest plots, no significant differences were observed in any of the outcomes investigated between the study conducted by Chen et al. and the other series included in this meta-analysis.[12,14,32,33] This finding may be attributed to the data sources used in some of the analyzed studies, as national registries such as the IRIS or the Swedish National Cataract Registry encompass postsurgical outcomes of procedures performed by both experienced specialists and trainees.

Although these limitations might be mitigated by randomized controlled studies, only 3 RCTs were included in our analysis.[64–67] This evidence likely reflects the restrictions placed on studies by regulatory bodies such as institutional review boards. In addition, designing trials that are large enough to be sufficiently powered to provide accurate estimates on the most fearful but uncommon complications of cataract surgery, such as TASS and endophthalmitis, have proven to be challenging. In the context of clinical trials, a standardized approach reporting the efficacy and safety outcomes of cataract surgery is warranted, as well as metrics from patient-reported outcome measures. In addition, although a recent independent stakeholder meeting in the United Kingdom pointed out that "cost savings to health care that may occur following ISBCS may be considered a secondary benefit," we believe that a robust, cost-effectiveness analysis based on quality-adjusted life years might be a helpful tool to explore the eventual additional benefits of ISBCS.[68]

Nonetheless, it should be noted that all the included RCTs excluded patients and eyes at high risk for surgical complications. Therefore, the results provided by this meta-analysis should be cautiously interpreted because they are not fully representative of all types of patients and eyes.

Although DSBCS continues to represent the most common approach for cataract surgery in many parts of the world, it must be recognized that a paradigm shift has begun. This is mainly due to the escalating burden of the cost of health care and the ever-growing competing demands placed on limited resources but also by the obvious benefits for our patients undergoing ISBCS and its very rare risks when surgery is conducted in a proper and organized manner. As reported in the last statement from the International Society of Bilateral Cataract Surgeons, "ISBCS is no longer rare and has been accepted, in most of the world, as being equally as effective as DSBCS with many advantages."[69] The results of our meta-analysis, the largest to date to analyze the safety and efficacy profile of ISBCS, substantiate this statement. However, we accept that some controversies will remain, which can be at least part attributed to the gravity of a rare complication that could cause potential blindness and its obvious emotional nature. The concern for a complete loss of sight due to ISBCS is a justifiable fear. In addition, the lack of approvals by nation-specific ophthalmology boards poses another major obstacle to the widespread adoption of ISBCS. While awaiting other data, for the surgeons already performing ISBCS, a thorough risk-assessment during evaluation of suitable surgical candidates, effective counseling and communication with patients, and an adherence to proposed guidelines should be mandatory to guarantee the highest standard of care for our patients.[42]

### WHAT WAS KNOWN

- Cataract is the leading cause of blindness worldwide and the second cause of vision impairment in adults aged 50 years and older.
- Although the bilateral cataract extraction procedure is generally performed in separate days (ie, DSBCS), a new alternative approach involves operating the 2 eyes in the same surgical session (ie, ISBCS).

### WHAT THIS PAPER ADDS

- This is the first largest study to date showing that the safety and efficacy profile of ISBCS is similar to the one of the more commonly performed DSBCS.
- Although the pooled analysis of nonrandomized studies did find ISBCS to carry an increased 1.3 risk of intraoperative posterior capsule rupture, the quality of this evidence was rated as low.
- These findings indicate that ISBCS is a reasonable approach in selected patients with bilateral visually significant cataract after counselling regarding risks and benefits.

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