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RESEARCHARTICLE

Comparison offemtosecond laser-assisted cataractsurgeryandconventional phacoemulsification oncorneal impact:A meta-analysis andsystematic review

[a1111111111](http://crossmark.crossref.org/dialog/?doi=10.1371/journal.pone.0284181&domain=pdf&date_stamp=2023-04-14) [a1111111111](http://crossmark.crossref.org/dialog/?doi=10.1371/journal.pone.0284181&domain=pdf&date_stamp=2023-04-14) [a1111111111](http://crossmark.crossref.org/dialog/?doi=10.1371/journal.pone.0284181&domain=pdf&date_stamp=2023-04-14) [a1111111111](http://crossmark.crossref.org/dialog/?doi=10.1371/journal.pone.0284181&domain=pdf&date_stamp=2023-04-14) [a1111111111](http://crossmark.crossref.org/dialog/?doi=10.1371/journal.pone.0284181&domain=pdf&date_stamp=2023-04-14)

**HanleWang**☯**,XinyiChen**☯**,JingjieXu**☯**,KeYa**[**oID**](https://orcid.org/0000-0002-6764-7365)**¤\***

EyeCenteroftheSecondAffiliatedHospital,MedicalCollegeofZhejiangUniversity,Hangzhou,China

☯Theseauthorscontributedequallytothiswork.

¤ Currentaddress:EyeCenteroftheSecondAffiliatedHospital,ZhejiangUniversitySchoolofMedicine, Hangzhou,China

\*xlren@zju.edu.cn

Abstract

OPENACCESS

**Citation:**WangH,ChenX,XuJ,YaoK(2023) Comparisonoffemtosecondlaser-assisted cataractsurgeryandconventional phacoemulsificationoncornealimpact:Ameta-analysisandsystematicreview.PLoSONE18(4): e0284181.[https://doi.org/10.1371/journal.](https://doi.org/10.1371/journal.pone.0284181) [pone.0284181](https://doi.org/10.1371/journal.pone.0284181)

**Editor:**AndrzejGrzybowski,UniversityofWarmia, POLAND

**Received:**November20,2022

**Accepted:**March26,2023

**Published:**April14,2023

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**DataAvailabilityStatement:**Allrelevantdataare withinthepaperanditsSupportinginformation files.

**Funding:**Thisworkwasfinanciallysupportedby theNationalNaturalScienceFoundationofChinain theformofgrants(82070939and81870641) awardedtoKY.Thisworkwasalsofinancially supportedbytheKeyResearchandDevelopment ProjectofZhejiangProvinceintheformofagrant

(2020C03035)awardedtoXC.Thisworkwasalso

Thismeta-analysisaimstocomparecornealinjuriesandfunctionafterfemtosecondlaser-assistedcataractsurgery(FLACS)andconventionalphacoemulsificationsurgery(CPS).A comprehensiveliteraturesearchofPubMed,EMBASE,andtheCochraneControlledTrials Registerwasconductedtoidentifyrandomizedcontrolledtrials(RCT)andhigh-qualitypro-spectivecomparativecohortstudiescomparingFLACSwithCPS.Endothelialcelllossper-centage(ECL%),centralcornealthickness(CCT),endothelialcelldensity(ECD),endothelial cellloss(ECL),percentageofthehexagonalcell(6A),andcoefficientofvariance(CoV)were usedasanindicatorofcornealinjuryandfunction.Totally42trials(23RCTsand19prospec-tivecohortstudies),including3916eyes,underwentFLACS,andatotalof3736eyesunder-wentCPS.ECL%issignificantlylowerintheFLACSgroupat1–3days(P=0.005),1week (P=0.004),1month(P<0.0001),3months(P=0.001),and6months(P=0.004)aftersur-gerycomparedtoCPS.ECDandECLappearednostatisticallysignificantdifference betweenthetwogroups,exceptforthesignificantreductionofECDat3monthsintheCPS group(P=0.002).CCTwassignificantlylowerintheFLACSgroupat1week(P=0.05)and 1month(P=0.002)earlypostoperatively.Whileat1–3days(P=0.50),3months(P=0.18), and6months(P=0.11),therewasnodifferencebetweentheFLACSgroupandtheCPS group.Nosignificantdifferencewasfoundinthepercentageofhexagonalcellsandthecoef-ficientofvariance.FLACS,comparedwithCPS,reducescornealinjuryintheearlypostoper-ativeperiod.CornealedemarecoveredfasterintheFLACSgroupintheearlypostoperative period.Inaddition,FLACSmaybeabetteroptionforpatientswithcornealdysfunction.

**Introduction**

Cataract isoneofthemostcommon eyediseases andthemajorcause ofvisionlossworldwide

[1].Surgically removingtheopacity lensand replacingitwithanintraocular lensiscurrently

PLOSONE|<https://doi.org/10.1371/journal.pone.0284181>April14,2023 1/19

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financiallysupportedbytheNaturalScience FoundationofZhejiangProvinceintheformofa grant(LQ23H120005)awardedtoXC.Thefunders hadnoroleinstudydesign,datacollectionand analysis,decisiontopublish,orpreparationofthe manuscript.

**Competinginterests:**Theauthorshavedeclared

thatnocompetinginterestsexist.

Cornealimpactoffemtosecondlaser-assistedcataractsurgery

theonlytreatmentforcataracts[2].Sinceits inventioninthe1960s,phacoemulsification has continuedtoimproveandremained thebesttherapyforcataracts[3]. Femtoseconds werefirst appliedtopromotethekeystepsofphacoemulsification in2008[4],such ascornealincision, lensfragmentation, andanteriorcapsulotomy[5].Eversincethediscussiononthecomparison offemtosecond-laser assistedcataractsurgery(FLACS)withconventional phacoemulsification surgery(CPS) hasneverceased.Manystudies theseyears havesuggested theoptimization of FLACSforcataractsurgery, including enhancingthecircularityofcapsulotomy [6], reducing theeffectivephacoemulsification time(EPT) [7],and providingbetterIOLplacement[8].

Thetransparencyand barrierfunctionofthecorneaismainlysustained bythecorneal endothelium[9], composedofasinglelayeroftheendothelialcell.Thecornealendothelium hasnoregenerative capacity[10]. Oncesuffering fromaninjury,endothelial cellscannotpro-liferate[11],and thelossofendothelialcellsisirreversible. Thehealing proceduresoccurred as theremaining surrounding endothelial cellsenlarged andmigrated tocoverthedamagedarea [12].Asaresult,theendothelial cellswillincrease insize andalterinshapefromhexagonal to pleomorphic [13].This leadstoachange inthepercentageofhexagonal cells(6A) andcoeffi-cientofvariance (CoV), whichillustrate thefunctionoftheresidualendothelial cells.During cataractsurgery procedures, phacoemulsification mayincreasetheriskofendothelial cellloss [9].Ithaslongbeenshownthatphacoemulsification results inapproximately 4%-25% of endothelialcell loss[14,15].Thenegativeeffectofphacocataract surgeryonendothelium is multifactorial andlargelyduetothermal[16]and mechanical injury[17]. Ithasbeenproven tobeassociatedwith surgical instruments,phacoemulsification time,ultrasound energy, and contactwithlensfragments duringsurgery [17–19].Sincefemtosecond lasers arethoughtto modifythesurgery procedureand lessentheusageofultrasound, theeffectofthis technique ontheendotheliumisofconcern.

Thecornealindicatorsusedinprevious meta-studies wereinadequate, and theincluded articleswerenotrigorousenough. Arecentlypublished meta-analysis selectedendothelial cell loss(ECL)andcentralcornealthickness (CCT)asindicators toevaluatecornealdamage. Kolb,etal.,inthemeta-analysis, notedasignificant ECL declineintheFLACSgroup1–3 monthspostoperatively, whiletherewasnosignificant difference within1weekandover6 months.CCTwassignificantly higher intheCPSgroupintheearlytime. Laterinthe6 months,thedifferencedecrease [20].Itwasworthmentioning thatthispapernotonly included prospective butalsoretrospective studies,which arenotasreliable asprospective studies andmayleadtogreater bias.Incontrast,Chenetal.proposed in2021[21]thatECL wasconsistently significantly lowerthanCPSintheFLACS groupinthefirstweekaftersur-gery.Thestudy analyzedRCTsonly,butthereweremultiplemistakesintheinclusion ofthe article.So,wesupposed itisnotcredibleenough. BesidesECLandCCT, thereareothercor-nealindicators. Asearlyas2016, Chenetal.[22]used theendothelial celllossrate(ECL%)to measurethedamagetothecornealendotheliumandconcluded thatthedifference persists aftersurgeryfrom1weekto3months. ECL% istheratioofthenumberofendothelial cells losstopreoperative endothelial cells,which eliminates thedifference frombaselineandthere-foremaybemorestatistically significant. However,thesamplesizewassmall atthetime,and newrelatedstudies havebeenpublishedinrecentyears.Inaddition,themorphology ofthe remaining cornealendothelialcellswasalsoofourinterest. Itisrepresented by6Aand CoV, indicatingthefunctionoftheresidualendothelial cells.Cornealinjuryisanimportant effect ofcataractsurgery andiscloselyrelatedtopostoperative visualquality.Former studieshad onlydiscussed 1–2cornealindicators. Inourstudy,avarietyofcornealindicators were selectedtocomprehensively evaluate thepostoperative cornealcondition. This meta-analysis aimedtocompare cornealimpactand functionafterFLACSandCPS toprovide areference

forclinical application.

PLOSONE|<https://doi.org/10.1371/journal.pone.0284181>April14,2023 2/19

PLOS ONE Cornealimpactoffemtosecondlaser-assistedcataractsurgery

**Materialsandmethods** **Searchstrategy** **andinclusioncriteria**

The study followed the PRISMA guidelines (Preferred Reporting Item for Systematic Reviews and Meta-Analysis). PubMed, EMBASE, and Cochrane Library were searched by keywords: “femtosecond” OR “Femtolaser” AND “cataract” in full text. Complete and pub-lished clinical prospective trials comparing FLACS and CPS up to date December 31, 2021, were included. Reviews, conference abstracts, case reports, letters, correspondence articles, and editorials were excluded. The researches that combined with other ophthalmic surgery were excluded. Involved studies should meet the criteria as follow: 1) prospective random-ized control trials orhigh-quality comparative cohort studies; 2) published inEnglish or Chi-nese; 3) compared clinical indicators of patients undergoing simple cataract surgery with and without femtosecond laser assistant; 4) contains at least one indicator of ECD, ECL, ECL %, CCT, CoV, 6A.

**Screeningprocess**

Studiesscreening werecarriedoutbytwoauthors (HL.W andJJ.X)independently.Titlesand abstractswerereadtoscreenforqualified studies, andfull-textreading wasperformedwhen necessarytodetermineeligibility forinclusion criteria.Articles indisagreement werecon-firmedbyathirdauthor(XY. C)afterdiscussion.

**Qualityassessment**

The cohort studies were assessed by Newcastle-Ottawa Scale (NOS) [23]. The NOS is an

8-stars scale based on patient selection (four stars), comparability (one star), and outcomes (three stars). Cochrane Collaboration’s tool for risk of bias [24] was applied to evaluate the quality of included RCTs by two independent authors (HL. W, JJ. X), which had random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases.

**Dataextractionandoutcomemeasurements**

Astandard dataform wasused intheextractionprocess, including thebasicinformation such astitle,authors,years, experimentaldesign,samplesize,clinical indicators, etc.Allthedis-agreementswerediscussedand solvedbeforedataanalysis andallofthedatawasdouble-checkedbyasecondreviewer. Cornealendothelium-related clinicalindicators atdifferent postoperative timepoints wererecorded withmean andstandard deviation. Whenstandard deviationwasnotreported, datawereruledout.Dataexpressed asmediansandquartiles were convertedtomean andstandarddeviation byLuo’sformula[25].Data containing subgroups inFLACS orCPSwerecombined.

**Dataanalysis**

RevMansoftware (version5.4;CochraneCollaboration, Oxford,UnitedKingdom)wasused instatistical analyses.Thecornealindicators wererecorded incontinuous datapresented by weighted meandifferences(WMDs) with 95%CIs.Statistical heterogeneity wascalculated usingthechi-square testand I2statistics, withI2measuresmorethan50%beingattributedto strongheterogeneity.Whenheterogeneity wasdemonstrated, random-effects models were used,otherwisefixed-effect models.Itwasregardedasastatistically significant difference betweenFLACS andCPSwhenthePvaluewaslessthan0.05.Sensitivity analysis assessedhow

PLOSONE|<https://doi.org/10.1371/journal.pone.0284181>April14,2023 3/19

PLOS ONE Cornealimpactoffemtosecondlaser-assistedcataractsurgery

theresultswould havechanged ifasingle studyhadbeenomittedbyasingle-study deletion analysis.

**Results** **Literatureresearchandtrailscharacteristics**

Atotalof3281studies wereidentified originally. Onethousandsixhundredtenduplicates werediscarded. Onethousandsixhundredseventy-oneleftstudies werescreened bytitleand abstract.Afull-text examination wasconductedwhennecessary. Afterexcluding allresearch thatdid notmeet thecriteria,42[26–67]trialsremained (Fig1).Oftheincluded studies,23 wereRCTs,and19werecomparative cohort studies.Totally3916eyesunderwent FLACS,and 3736eyesunderwent CPS.Characteristics ofallthetrialsarerecordedinTable1.Thequality assessmentofRCTsispresentedinS1andS2Figs,whilethatofthecomparative cohortisin S1Table.

**Fig1.** **FlowdiagramforidentificationofrelevantstudiesonthecornealimpactofFLACSandCPS.**

<https://doi.org/10.1371/journal.pone.0284181.g001>

PLOSONE|<https://doi.org/10.1371/journal.pone.0284181>April14,2023 4/19

PLOS ONE Cornealimpactoffemtosecondlaser-assistedcataractsurgery

**Table1.** **Characteristicsoftheincludedstudies.**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **author** | **year** | **study** **design** | **FLACSplatform** | **country** | **age** **(mean±sd)** | | **sex** **(male:** **female)** | | **no.** **of** **eye** | | **follow-up** |
| **FLACS** | **CPS** | **FLACS** | **CPS** | **FLACS** | **CPS** |
| Abell | 2014 | cohort | Catalys | Australia | 72.4±10.1 | 72.6±9.8 | 135:270 | NA | 405 | 215 | 6m |
| Abell | 2013 | cohort | Catalys | Australia | 72.8±10.5 | 71.8±10.8 | 69:81 | 23:28 | 150 | 51 | 3w |
| Al-Mohtaseb | 2017 | cohort | LenSx&catalys | USA | 66.69±8.64 | 69.51±8.13 | 26:34 | 29:31 | 60 | 60 | 1m |
| Bascaran | 2018 | RCT | Victus | Spain | 70.44±6.86 | | 36:56 | | 92 | 92 | 6m |
| Cavallini | 2019 | cohort | LDV Z8 | Italy | 75.45±7.88 | 75.06±9.32 | 19:30 | 16:41 | 80 | 80 | 3m |
| Chee | 2021 | RCT | Victus | Singapore | 72.3±9.5 | 75.8±8.0 | 24:21 | 27:21 | 45 | 48 | 1m |
| Chen | 2017 | cohort | LenSx | China | 68.38±8.45 | 70.27±8.53 | 18:29 | 21:27 | 47 | 48 | 3m |
| Chlasta-Twardzik | 2019 | RCT | LDV Z8 | Pland | 79.08±5.51 | 74.59±8.10 | 6:20 | 18:43 | 26 | 61 | 6m |
| Conrad-Hengerer | 2013 | RCT | Catalys | Germany | 70.9 | | 27:46 | | 73 | 73 | 3m |
| Day | 2021 | RCT | LDV Z8 | UK | 68±10 | | 48:52 | | 392 | 393 | 12m |
| Day | 2020 | RCT | LDV Z8 | UK | 68±10 | 68±10 | 182:210 | 192:201 | 392 | 393 | 3m |
| Day a | 2020 | RCT | LDV Z8 | UK | NA | NA | NA | NA | 292 | 311 | 12m |
| Duan | 2017 | cohort | LenSx | China | NA | NA | NA | NA | 74 | 74 | 3m |
| Dzhaber | 2020 | RCT | LenSx | USA | 68.3±9.1 | | NA | NA | 67 | 67 | 3m |
| Fan | 2018 | RCT | LenSx | China | 66.1±9.2 | 63.9±12.5 | 3:7 | 2:6 | 16 | 15 | 12m |
| Gao | 2018 | cohort | NA | China | 66.32±6.12 | 65.12±7.15 | 28:31 | 25:22 | 59 | 47 | 3m |
| Hansen | 2020 | RCT | LenSx | USA | 68.7±8.5 | 69.0±14.1 | 27:44 | 25:39 | 64 | 71 | 3m |
| Kanellopoulos | 2016 | cohort | LenSx | Greece | 67.3±11.99 | 69.92±11.73 | 27:40 | 29:37 | 67 | 66 | 12m |
| Kelkar | 2020 | cohort | Catalys | India | 64.5±9.7 | 65.4±8.4 | 56:33 | 57:41 | 89 | 98 | 6m |
| Khan | 2017 | RCT | LenSX | Pakistan | NA | NA | 23:25 | | 25 | 25 | 1m |
| Krarup | 2019 | RCT | LensAR | Denmark | NA | NA | 52:56 | | 81 | 81 | 6m |
| Krarup | 2021 | RCT | LensAR | Denmark | 75 | | 17:17 | | 31 | 31 | 6m |
| Krarup | 2014 | cohort | LensAR | Denmark | NA | NA | NA | NA | 47 | 47 | 3m |
| Liu | 2016 | cohort | NA | China | 50.1±3.3 | 49.6±2.6 | 15:6 | 14:7 | 21 | 21 | 12m |
| Liu | 2021 | RCT | LDV Z8 | Singapore | 69.5±6.9 | | 48:37 | | 78 | 78 | 12m |
| Mencucci | 2020 | cohort | LenSx | Italy | 73.9±7.7 | 74.5±5.8 | NA | NA | 20 | 20 | 6m |
| Mursch-Edlmayr | 2017 | RCT | Victus | Germany | 72±6 | | 31:19 | | 50 | 50 | 6m |
| Niu | 2018 | cohort | LenSx | China | 67.12±5.64 | 66.39±5.23 | 32:38 | 35:47 | 107 | 126 | 3m |
| Oka | 2021 | RCT | LenSx | Japan | 73.4±6.5 | | 20:33 | | 53 | 53 | 7m |
| Pisciotta | 2018 | cohort | LDV Z8 | Italy | 74.07±8.48 | 75.72±9.16 | 10:20 | 8:22 | 30 | 30 | 3m |
| Ranjini | 2017 | cohort | LenSx | India | NA | NA | NA | NA | 55 | 55 | 1m |
| Reddy | 2021 | cohort | Catalys | India | 59.5±9.5 | 58.25±10.1 | 11:9 | 22:18 | 20 | 40 | 5w |
| Roberts | 2019 | RCT | LenSx | UK | 69.9±10.9 | 70.5±9.8 | 100:100 | 82:118 | 200 | 200 | 1m |
| Schargus | 2015 | RCT | Catalys | Germany | 71.8 | | 15:22 | | 37 | 37 | 6m |
| Schroeter | 2021 | RCT | LenSx | Switzerland | 70.5±8.3 | 69.6±8.1 | 31:34 | 27:38 | 65 | 65 | 3m |
| Shi | 2020 | RCT | LenSx | China | 61.09±10.87 | | 144:134 | | 150 | 150 | 3m |
| Takacs | 2012 | RCT | LenSx | Hungary | 65.81±12.42 | 66.93±10.99 | 10:28 | 15:23 | 38 | 38 | 1m |
| Vasavada | 2019 | RCT | LenSx | India | 67.21±11.11 | 63.70±11.84 | NA | NA | 91 | 91 | 6m |
| Wu | 2017 | RCT | NA | China | 62.9±4.8 | 61.7±5.2 | NA | NA | 85 | 105 | 3m |
| Yang | 2019 | cohort | LenSx | China | 60.51±3.41 | 61.43±3.46 | 25:22 | 24:23 | 47 | 47 | 3m |
| Yu | 2015 | cohort | LensAR | China | 62.3±11.6 | 56.5±16.6 | NA | NA | 25 | 29 | 3m |
| Yu | 2016 | cohort | LenSx | China | 69.66±9.27 | 72.74±8.83 | 33:37 | 23:31 | 70 | 54 | 6m |

<https://doi.org/10.1371/journal.pone.0284181.t001>

**Endothelialcelllossrate(ECL%)**

Fifteenstudies reported postoperative ECL%.FLACSgroup demonstrated significantly lower ECL% at1–3days (WMD:-3.95,95%CI:-6.70,-1.21,P=0.005),1week(WMD:-3.09,95%CI:

PLOSONE|<https://doi.org/10.1371/journal.pone.0284181>April14,2023 5/19

PLOS ONE Cornealimpactoffemtosecondlaser-assistedcataractsurgery

-5.19,-0.98,P=0.004),1month(WMD:-3.14,95%CI:-4.17,-1.57,P*<*0.0001), 3months (WMD:-4.72,95%CI:-7.62,-1.82,P=0.001)and6months(WMD:-1.60,95%CI:-2.70,-0.50, P=0.004)postoperatively (Fig2).

**Endothelialcelldensity(ECD)andEndothelialcellloss(ECL)**

Therewasnosignificant difference inECD at1–3days (WMD:-12.40, 95%CI:-109.56, 84.76, P=0.80),1week(WMD:10.58, 95%CI:-64.10, 85.26,P=0.78),1month(WMD:21.14, 95% CI:-77.01,119.29,P=0.67),6months(WMD:-1.23, 95%CI:-68.27, 65.81,P=0.97)and12 months(WMD:6.80, 95%CI:-52.86, 66.47,P=0.82)aftersurgerybetween twogroups, andsig-nificantdifference at3months(WMD: 84.49,95%CI:31.25, 137.73,P=0.002,Fig3).

Similarly, therewasnosignificant difference inECL at1–3days (WMD:50.95,95%CI: -24.92,126.82,P=0.19),15–40days (WMD:11.49,95%CI:-67.40,90.38,P=0.78),2–3 months(WMD:2.81, 95%CI:-32.61,38.23,P=0.88),and6months(WMD:-19.72,95%CI: -85.63,46.19,P=0.56)aftersurgery betweentwogroups(Fig4).

**Centralcornealthickness(CCT)**

Fifteenstudies reported postoperative CCT.Nostatistically significant difference wasfound betweenFLACS andCPSat1–3days(WMD:-3.98,95%CI:-15.61,7.64,P=0.50) aftersur-gery.Significantly lowerCCTwasobservedinFLACScompared toCPSat1week(WMD: -6.17,95%CI:-12.29,-0.06,P=0.05)and1month(WMD:-6.86,95%CI:-10.15,-2.04, P=0.002).Whereas,laterat3months(WMD: -4.99,95%CI:-12.28,2.30,P=0.18)and6

months(WMD:-3.44,95%CI:-7.70,-0.82,P=0.11),therewasnostatistically significant dif-ferencebetween twogroups (Fig5).

**Percentageofhexagonalcells(6A)**

Aswasreportedbysevenresearches, nosignificant difference wasfoundbetween FLACSand CPSgroupat1month(WMD:-0.36,95%CI:-3.04,2.32,P=0.79),3months(WMD:0.25, 95%CI:-1.42,1.92,P=0.77)and6months(WMD:-0.58,95%CI:-1.79,-0.62,P=0.34,Fig6).

**Coefficientofvariance(CoV)**

Five researches reported CoV were enrolled. No significant difference was found between the two groups at 1 month (WMD: -0.76, 95%CI: -1.99, 0.48, P = 0.23), 3 months (WMD: 0.47, 95%CI: -0.78, 1.73, P = 0.46) and 6 months (WMD: 0.35, 95%CI: -0.64, 1.34, P =0.48, Fig 7).

**Discussion**

Thismeta-analysis study showedtheimpact ofFLACSonpostoperative cornealendothelial injurycomparedtoCPS.FLACSreducedECL% significantly ateachtimepointpostopera-tively.AndCCTfavoredFLACSat1weekand1monthearly aftersurgery.

TheECL% oftheFLACSgroupwassignificantly lowerthanthatoftheCPSgroupateach timepointduring6monthspostoperatively, indicating thatFLACS hasreducestheinjuryof cornealendothelialcells.Thiswasconsistent withpreviously publishedmeta-analysis [22]. Cataract surgical injurymayresultinadecrease incornealendothelial cells,thusaffecting the functionofthecornea,andleading tocornealedema.Severalfactorshadbeenreportedtobe involved inendothelial cellloss,suchasultrasound energy, phacoemulsification time, irriga-tiontime, andusageofbalancedsaltsolution duringoperation[68–70].InFLACS,thenucleus ofthelensispre-fragmented byafemtosecond laserinsteadofmanipulation. This allowsless

PLOSONE|<https://doi.org/10.1371/journal.pone.0284181>April14,2023 6/19

PLOS ONE Cornealimpactoffemtosecondlaser-assistedcataractsurgery

**Fig2.** **ForestplotofpostoperativeECL%betweenFLACSandCPSatA.1–3days,B.1week,C.1month,D.3** **months,andE.6months.**

<https://doi.org/10.1371/journal.pone.0284181.g002>

applicationofultrasound energyandirrigating solutionduringcataract surgery[29], thereby reducing itsdamagetoendothelial cells.Aswasreported byAbell[27]andOshika [71],the effectofFLACSmaybeduetothelowerrequirementofeffectivephacoemulsification time (EPT),ultrasound energy, andirrigationfluid comparedtoCPS.

PLOSONE|<https://doi.org/10.1371/journal.pone.0284181>April14,2023 7/19

PLOS ONE Cornealimpactoffemtosecondlaser-assistedcataractsurgery

**Fig3.** **ForestplotofpostoperativeECDbetweenFLACSandCPSatA.1–3days,B.1week,C.1month,D.3** **months,E.6months,andF.12months.**

<https://doi.org/10.1371/journal.pone.0284181.g003>

Lacking regenerative ability,thetotalamountofcellswasnolongercompensated after endothelialcell loss.Instead,migration andenlargement ofresidualcellsoccurasacorneal repairingprocedure [9].Theremaining cellsmigrate totheinjured area,resultinginagradual increaseinendothelial celldensitywhenmeasuring atthecenterofthecornea[12]. Thispro-cesstakesmonths[72], therefore,lowerECL%onthefirstdayaftersurgeryindicated less

PLOSONE|<https://doi.org/10.1371/journal.pone.0284181>April14,2023 8/19

PLOS ONE Cornealimpactoffemtosecondlaser-assistedcataractsurgery

**Fig4.** **ForestplotofpostoperativeECLbetweenFLACSandCPSatA.1–3days,B.15–40days,C.2–3months,** **andD.6months.**

<https://doi.org/10.1371/journal.pone.0284181.g004>

damagetothecornealendotheliumintheFLACS group.Thelong-term follow-up(3months, 6months) inthegeneral population subgroup(S3Fig)showed nosignificant difference betweenthetwogroups.Itmeantthatthecornealendotheliumcanberepairedtoasimilar levelintheFLACSand CPSgroups.AndthelowECL% intheFLACSgroupat1weekand1 monthaftersurgery indicatedthatthecornealendothelial repairwasfasterintheFLACS group.

Differences inECL% at3and6monthsaftersurgery proposed apersistent effectofFLACS andCPSonthecornea, butwefoundthatthemainimpact maycomefrom studiestargeted to aspecific population.Subgroup analysis ofthegeneralpopulation revealedthatECL% at1–3 days,1week,and1monthintheFLACSgroupwasstillsignificantly lowerthantheCPS group,whilenosignificant differencewasfoundat3monthsand 6monthsaftersurgery. Fuch’ssyndrome orhardnuclearpatientswerenotincluded inthesubgroup. Thisresultsug-gestedthatdifferencesinECL% inlong-termfollow-uparemainlycaused byspecial popula-tions.Fuchs’endothelial cornealdystrophy patientswereinastateofcornealdecompensation

PLOSONE|<https://doi.org/10.1371/journal.pone.0284181>April14,2023 9/19

PLOS ONE Cornealimpactoffemtosecondlaser-assistedcataractsurgery

**Fig5.** **ForestplotofpostoperativeCCTbetweenFLACSandCPSatA.1–3days,B.1week,C.1month,D.3** **months,andE.6months.**

<https://doi.org/10.1371/journal.pone.0284181.g005>

PLOSONE|<https://doi.org/10.1371/journal.pone.0284181>April14,2023 10/19

PLOS ONE Cornealimpactoffemtosecondlaser-assistedcataractsurgery

**Fig6.** **Forestplotofpostoperative6AbetweenFLACSandCPSatA.1month,B.3months,andC.6months.**

<https://doi.org/10.1371/journal.pone.0284181.g006>

**Fig7.** **Forestplotofpostoperative6AbetweenFLACSandCPSatA.1month,B.3months,andC.6months.**

<https://doi.org/10.1371/journal.pone.0284181.g007>

PLOSONE|<https://doi.org/10.1371/journal.pone.0284181>April14,2023 11/19

PLOS ONE Cornealimpactoffemtosecondlaser-assistedcataractsurgery

preoperatively, withextremelylowbasal endothelial cellcount[73].InFan’sstudy,theECL% remained asignificant difference untiltheendpointoffollow-up(12months) [39].Andthe meanECL% intheCPSgroup(32.2%at12months) wasalsomuchhigher than4%-25%, whichwaspreviouslyreported inthegeneralpopulation [15].Additionally, patients withhard nuclearmaysuffer higherultrasound energyandprolonged phacoemulsification timetoman-ifestthedenscataract;thus,intraoperative endothelialcellsinjurywaseven moresevere[32]. Inthegeneralpopulation, theECL%wassimilar inthelong-term follow-upinFLACS and CPSgroups. Itimpliedthatthelong-term effectofFLACSandCPS arecomparable. Asforthe populationwith dysfunctional cornea,injurycausedbysurgerywillpersist[39].Thus, we stronglyrecommend thatFLACSmaybethesuperior optionforcornealdysfunction and hard nuclearpatients.

Contrary topreviouslypublished meta-analysis [20,21],ECD andECLdidnotshowsignif-icantdifferences acrossperiods.Itwaspossibly because thattheabsolute valueofendothelial cellsmaybeaffectedbythebaselinelevel(preoperative ECD), whiletheECL%canruleoutthe influence.ECL% isthepercentageofendothelial celllossinthepreoperative endothelial cell density, calculatedbytheformula: ECL%=((preoperative ECD-postoperative ECD)/preoper-ativeECD)\*100%.Compared withECD andECL,ECL%appears tobeless affectedbyinter-ferencefactors. Forexample, Al-Mohtaseb [28]reported thatbaseline ECDintheFLACS group(2,408.78 ±169.73)wassignificantly lowerthanthatoftheCPSgroup (2,486.29±154.37,P=0.03).Postoperatively, therewasnodifferenceinECDbetween thetwo groups (FLACS:2,254.84±264.46,CPS:2,255.53±262.93,P=0.49).However,ECL% favored theFLACSgroup (P=0.04).Althoughthepostoperative ECDwasthesame,therewerediffer-encesinthenumberofendothelial cellslossbetween thetwogroups; thus,theECDmay not beanaccuratereflection ofendothelialcellchange. ThesameistrueforECL,wherethesame numberofECLaccountsfordifferent ratioswhenthetwogroups areatdifferent baselines [42].Giventheseconditions, ECL%might beamoreobjective indicator torepresent endothe-lialcellchanges becausethepreoperative variance inECDwasremoved.

Inaddition,different surgical approaches, such asmanualorfemtosecond-assist corneal incision,canalsoinfluence theendothelium. Femtosecondincision wasthoughttocause fur-therdamagetothecornea[74]. Femtosecondlaseractsonthecapsular bagwhenpretreating cataracts.Whileinthestepoflaser-assisted cornealincision,thelaserenergydirectly conveys tothecornealendothelium[26].Furthermore, microbubbles arising fromlaser-induced cor-nealrupture caninfluence thesurfacetensionofendothelium andamplify thedamagetoit [75].However,somestudies lackedadescription ofthisstep;thus,itwasdifficult forustoper-formasubgroupanalysis ofcornealincisions.

Acrossalltimepoints,ECDat3monthsaftersurgerydifferedfromtheothers.Wenoticed studiesthatrecordedcornealdataonlyat3monthsaftersurgery[60,67],whichmightexerta largeimpactonthe3monthspostoperativeoutcomesofECD.AlthoughtheECDintheFLACS groupwassignificantlyhigherthanthatintheCPSgroup,thedifferencedisappearedwhenonly RCTswereincluded(S4Fig).Meanwhile,theheterogeneityintheRCTsubgroupdecreasedsig-nificantly(I2 =4%).RCTstudiesreducebiasduetorandomizedgroupingandareconsidered morereliablethancohortstudies.We,therefore,supposedthatthesubgroupresultsoftheRCT weremoreconvincingatthistimepoint.Atothertimepoints,therewasnosignificantdiffer-enceinECDbetweenthetwogroupswhenconsideringtheRCTstudiesonly(S4Fig).

CCTrepresents thedegree ofcornealedemaandisalsoanevaluationindex ofcorneal endothelialfunction [76].Ourstudydemonstrated nosignificant differenceinCCT1–3days afterFLACSandCPS,which indicatedsimilar cornealedemacaused bytwotypesofcataract surgery.This wasincontrast toearlier meta-analyses. However,weperformed asubgroup analysis ofthefemtosecond platform andfoundthatinstudies using theCatalys (Johnson&

PLOSONE|<https://doi.org/10.1371/journal.pone.0284181>April14,2023 12/19

PLOS ONE Cornealimpactoffemtosecondlaser-assistedcataractsurgery

JohnsonVisionCare, Inc.)femtosecond platform,CCTwassignificantly smaller intheFLACS group(S5Fig).Itmaybecausedbydifferentdockingmodes.InCatalysfemtosecondplatform, aliquidopticalimmersion interface (LOI)[77]isappliedtothedocking phase.Correspond-ingly,LenSxplatforms usecurvedcontactlensinterface[78].SinceLOIdoesnotdirectlycom-pressthecornea,itexertsless pressure,andconsequently, inducesless damagetotheshapeof thecornea[79]. Becauseofthefactabove,wesupposed Catalys performsabetter protective effectoncornealendotheliumsincethereisnodirectcontact withthecornea duringthefem-tosecond-laser period.Currently, therewasnostudyproposing thatCatalys laserplatform has betterendothelium protectionthanLenSx.Andsubgroupanalysesofplatforms atmoretime postoperatively hadnosignificant resultsduetothelimited numberofstudies acrossdifferent platforms.Welookforwardtomorestudies onthecornealeffectsoffemtosecond platformsin thefuture.CCTwassignificantly smaller thanCPSat1weekand 1month intheFLACS group,whiletherewasnosignificant differenceat3monthsand6months. Thisimpliedthat cornealedemaresolved fasterintheFLACS group,and thelong-term effectsofFLACS and CPSoncornealedemaweresimilar.

CoVand6Ademonstratedthatneitherprovedsignificantdifferencesatanytimepoint, indicatingasimilarmorphologicalchangeofendothelialcellsaftersurgery.Alterationincell shapeandsizeoccursduringcornealrepairment,andthesetwoindicatorsrepresentendothelial functionalcapacity.Itsuggestedthattherewasnodifferenceintheeffectofthetwosurgeries onthefunctionoftheresidualendothelialcells.Interestingly, asubgroupanalysisofSchroeter’s study[55]showedthatCoVdecreasedwhenEPTlessened.Althoughtheresultswerehighly consistent,thenumberofstudiesandthefollow-uptimepointsonthesetwoindicatorswere notrichenough.Therefore,morefollow-uparticlesandsubgroupanalysesarenecessary.

Inaddition,weshould alsonotethatsomereports havefollowed uponthelong-term effectsofFLACSandCPSforoneyear.Theresultsshowed thattherewasnosignificant differ-enceinalong-term vision, complications, andcornealeffectsbetweenthetwogroups [36,80]. ItisworthnotingthatFLACS hasahighereconomic cost,which mayalsobeaproblemtobe consideredwhenselecting surgical methods[81].

Unavoidably, therewerelimitations tothismeta-analysis. Firstly,thepostoperativefollow-uptimewasonly6months,which wasduetoinsufficient follow-updatabeyond6months. Welookforward tomorelong-term follow-uparticles.Secondly, theincluded studies were fromdifferent regions, usingdifferent CPSplatforms, implemented bydoctors ofvaryingpro-ficiency,making itdifficult tounifypatients’ preoperative baselines,resulting inincreased het-erogeneity.This meta-analysis wasrestrictedtodatafrompublished studies,soinformation biascouldnotbefullyruledoutifstudies withsmall sample-size orunpublisheddataexist. Andweonlyincluded clinicalstudies published inChinese andEnglish, whichmayleadto language bias.

**Conclusions**

Inconclusion, FLACSreducedcornealinjuryintheearlypostoperative period.Earlypostop-erativecornealedemarecovered fasterthanCPS.Forpatientswithfewer endothelialcells,itis stronglyrecommended toconsider FLACSfirst.

**Supporting** **information**

[**S1Fig.**](http://www.plosone.org/article/fetchSingleRepresentation.action?uri=info:doi/10.1371/journal.pone.0284181.s001)**Risk** **ofbiasgraph:** **Basedonresearchers’** **opinions** **abouteachriskofbiasitem,per-centagesarepresentedfor** **allincluded** **studies.**

(TIF)

PLOSONE|<https://doi.org/10.1371/journal.pone.0284181>April14,2023 13/19

PLOS ONE Cornealimpactoffemtosecondlaser-assistedcataractsurgery

[**S2Fig.**](http://www.plosone.org/article/fetchSingleRepresentation.action?uri=info:doi/10.1371/journal.pone.0284181.s002)**Assessment** **oftheriskof** **biasintheincluded** **RCTs.**Greencircle(+):Lowrisk,Red circle(−):Highrisk,?:Unclear.

(TIF)

[**S3Fig.**](http://www.plosone.org/article/fetchSingleRepresentation.action?uri=info:doi/10.1371/journal.pone.0284181.s003)**Forest** **plotofpostoperative** **ECL%in** **generalpopulation** **between** **FLACSandCPS** **atA.1–3days,B.1week,** **C.1month,D.3months,** **andE.6months.**

(TIF)

[**S4Fig.**](http://www.plosone.org/article/fetchSingleRepresentation.action?uri=info:doi/10.1371/journal.pone.0284181.s004)**Forest** **plotofpostoperative** **ECDbetweenFLACSand** **CPSthatonlyincluded** **RCTsatA.1–3days,** **B.1week,C.1month,** **D.3months,andE.6months.**

(TIF)

[**S5Fig.**](http://www.plosone.org/article/fetchSingleRepresentation.action?uri=info:doi/10.1371/journal.pone.0284181.s005)**Subgroup** **analysis** **ofpostoperative** **CCTbetween** **FLACSandCPS** **at1–3days.** (TIF)

[**S1Table.**](http://www.plosone.org/article/fetchSingleRepresentation.action?uri=info:doi/10.1371/journal.pone.0284181.s006)**TheNewcastle-Ottawa** **Scale(NOS)ofcohort** **studies.** (PDF)

[**S1Checklist.**](http://www.plosone.org/article/fetchSingleRepresentation.action?uri=info:doi/10.1371/journal.pone.0284181.s007)**PRISMA2020checklist.** (DOCX)

**AuthorContributions**

**Conceptualization:** HanleWang,XinyiChen, JingjieXu,KeYao.

**Datacuration:** HanleWang, XinyiChen,JingjieXu.

**Formalanalysis:**HanleWang,XinyiChen, JingjieXu.

**Funding** **acquisition:** HanleWang,KeYao.

**Investigation:** HanleWang,XinyiChen,KeYao.

**Methodology:** HanleWang,XinyiChen,JingjieXu.

**Projectadministration:** HanleWang,JingjieXu.

**Resources:** HanleWang, JingjieXu.

**Software:**HanleWang,JingjieXu.

**Supervision:** HanleWang,JingjieXu.

**Validation:** HanleWang.

**Visualization:** HanleWang.

**Writing** **–original** **draft:**HanleWang.

**Writing** **–review&editing:** XinyiChen,JingjieXu,KeYao.

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