STUDY PROTOCOL

REVISED Does the phaco TIp position during clear corneal Phacoemulsification Surgery adversely affect corneal endothelium? TIPS study protocol for a randomised, triple-masked, parallel-group trial of bevel-up versus bevel-down phacoemulsification [version 2; peer review: 1 approved, 1 approved with reservations]

Soujanya Kaup[1], Siddharudha Shivalli[2], Chinnappa Ajjinicanda Ganapathi[3], Cynthia Arunachalam[1], John Buchan[4], Suresh Kumar Pandey[5], Krishna Prasad Kudlu[3]

[1]Department of Ophthalmology, Yenepoya Medical College Hospital, Yenepoya Deemed to be University, Mangalore, Karnataka, 575018, India
[2]Department of Medical Statistics, London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT, UK
[3]Department of Ophthalmology, Netra Jyothi Charitable Trust Hospital, Udupi, Karnataka, 576101, India
[4]International Centre for Eye Health, London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT, UK
[5]Department of Ophthalmology, SuVi Eye Institute and Lasik Laser Center, Kota, Rajasthan, 324005, India

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Abstract

Introduction: Globally, at least 30 million cataract surgeries are required annually to prevent cataract-related blindness. Corneal endothelial decompensation is one of the most common causes of poor visual outcome following cataract surgery, particularly in those with predisposing factors. The increasing ageing population and reduced visual impairment threshold for cataract surgery have resulted in rising cataract surgical rates and hence, an increase in corneal endothelial decompensation is expected. The role of phaco tip position on corneal endothelial damage is ambiguous. Previous studies have reported contradictory results and were also underpowered to detect a significant difference due to small sample sizes. With no consensus regarding the most cornea-friendly phaco tip position (bevel-up versus bevel-down) during phacoemulsification, we propose a randomised clinical trial with a robust design using direct chop phaco-technique.

Objective: To compare the effect of phaco tip position (bevel-up vs.

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1. **Peter A Mattei**, University G. D'Annunzio Chieti-Pescara, Chieti, Italy

2. **Anthony Vipin Das**, LV Prasad Eye Institute, Hyderabad, India

Any reports and responses or comments on the

bevel-down) on corneal endothelial cell count during phacoemulsification.
Methods: A randomised, multicentre, parallel-group, triple-masked (participant, outcome assessor, and statistician) trial with 1:1 allocation ratio is proposed. By adopting stratified randomisation (according to cataract grade), we will randomly allocate 480 patients aged >18 years with immature cataract into bevel-up and bevel-down groups at two centres. History of significant ocular trauma, previous intraocular surgery, shallow anterior chamber, low endothelial cell count, pseudoexfoliation syndrome, intraocular inflammation, and corneal endothelial dystrophy are the key exclusion criteria. The primary outcome is postoperative endothelial cell count at one month. Secondary outcomes are central corneal thickness on postoperative days 1, 15, and 30, and intraoperative complications.
Trial registration: Clinical Trial Registry of India CTRI/2019/02/017464 (05/02/2019).

Keywords
Endothelial cell loss, phacoemulsification, phacoemulsification/complication, pseudophakic bullous keratopathy, Phaco-tip, bevel-up, bevel-down, specular microscopy

article can be found at the end of the article.

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Corresponding authors: Soujanya Kaup (drsoujanyak@gmail.com), Siddharudha Shivalli (shivalli.bhu@gmail.com)

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REVISED **Amendments from Version 1**

This updated version includes COVID-19 impact, and adaptions (with approval from ethics committees) in the trial, and edits addressing the reviewers' comments.

Any further responses from the reviewers can be found at the end of the article

Introduction

Cataract causes blindness or moderate to severe visual impairment in about 62.5 million people globally[1]. Each year, at least 30 million cataract surgeries are required to prevent cataract-related blindness[2]. Owing to the increasing burden of cataract (due to the growing ageing population of the world[3] and reduced visual impairment threshold for surgery[4],) the number of cataract surgeries performed is likely to increase[2,5]. Phacoemulsification is the most commonly performed cataract surgery in developed countries and is rapidly increasing in developing countries like India[6].

Corneal endothelium pumps fluid out of the corneal stroma, prevents the development of corneal oedema and thus maintains corneal transparency[7]. Normally, about 0.3–0.6% of the endothelial cells are lost every year[8,9]. Corneal endothelial cell loss is likely to increase (in varying amounts) after any intraocular surgery[10]. Following injury, endothelial cells increase in size and change from a hexagonal to pleomorphic shape[9]. Persistent corneal oedema can occur if the injury causes significant endothelial cell loss (below the critical density), necessitating corneal transplantation.

Corneal endothelial decompensation is a common cause of post-operative poor vision following cataract surgery with a reported incidence of 0.5–2% of cataract surgeries[11,12]. Phacoemulsification, particularly in those with certain predisposing factors, results in significant endothelial cell damage and loss, with corneal decompensation[13] and is one of the leading indications for corneal transplant across the globe. Corneal decompensation constitutes 28% of all the keratoplasties in North America; 20.6% in Europe; 21.1% in Australia; 13.6% in the Middle East; 15.5% in Asia, and 18.6% in South America[14]. Hence, with an increase in the number of cataract surgeries, a significant increase in the incidence of corneal endothelialdecompensation is anticipated.

Old age, increased nucleus density and high ultrasound energy increase the risk of endothelial cell loss during phacoemulsification[13,15,16]. To minimise the corneal endothelial cell loss, various modulations in phaco platforms and different phaco-surgical techniques are introduced. The magnitude of endothelial cell loss is directly related to the amount of ultrasoundenergy used[16]. Hence, power modulation by various means (e.g. microburst techniques) is a provision with most phaco machines to reduce the amount of ultrasound energy. Additionally, different phaco techniques that decrease the amount ofultrasound energy used are employed[17–21].

Despite advancement in the phacoemulsification technique, corneal endothelial damage continues to be a key concern. The proportion of endothelial cell loss that is accounted for by the choice of phaco tip position is uncertain. It is speculated that the phaco tip, considered to be the source of heat, when kept away from the corneal endothelium with the bevel-up technique might result in minimal cell loss[22]. However, in this position, the cavitational energy is directed towards the endothelium, which may have a negative impact. It is also possible that the bevel-down technique is more cornea-protective, with better contact between the phaco tip and the nucleus, making power delivery and aspiration more effective[23,24].

Previously published studies investigating the impact of phaco tip position on the endothelium have reported contradictory results[22,25,26]. Moreover, these studies were underpowered to detect a significant difference due to small sample sizes (n= 25 to 30 in each group). In an artificial eye model study, Frohn *et al.* reported that there was no significant difference (n=30 experiments, p= 0.7869) in the amount of ultrasound waves reaching the cornea in bevel-up and bevel-down positions[27]. However, an artificially controlled environment study might not mirror natural eye conditions.

Joshi *et al.* compared different phaco parameters of 'phacoemulsification with a 0-degree phaco tip' and '30-degree phaco tip with combination of bevel-up and bevel-down phacoemulsification', and found no significant difference in both groups. However, they did not compare the effect of these manoeuvres on corneal endothelial cell loss. Hence, there is no consensus regarding the most cornea friendly phaco tip position during phacoemulsification[28].

The authors were previously conducting a clinical trial exploring the effect of phaco tip position on central corneal thickness (CCT) during phacoemulsification[29]. CCT was the primary outcome as no specular microscope was available. CCT is not a definitive measure of corneal endothelial cell loss, as it is affected by other factors such as glucose and HbA1c levels. CCT is also known to display diurnal variation; being thickest in the morning and gradually thinning as the day progresses[30–33].

To answer this long-standing clinical question, we propose a randomised clinical trial with a robust study design using direct chop phacoemulsification technique and specular microscopy, which can non-invasively analyse the morphology of endothelial cells.

Objective

To compare the effect of phaco tip position (bevel-up vs. bevel-down) on corneal endothelial cell count during phacoemulsification.

Trial design and registration

Randomised, multicentre, parallel-group, triple-masked (participant, outcome assessor, and statistician) trial with 1:1 allocation ratio. The trial is prospectively registered in the

Clinical Trial Registry of India (CTRI/2019/02/017464; registered on 05/02/2019) with all items from the World Health Organization Trial Registration Data Set. This is trial protocol version 4 (15/09/2018); the previous three versions have not been published elsewhere.

Methods

Ethical statement

The study protocol was approved by the ethics committees of Yenepoya (Deemed to be) University, Mangalore, India [YEC-1/217/2019] and Manipal Academy of Higher Education, Manipal, India [MAHE/ EC/05-19/06]. Any modifications in the trial protocol would require ethics committee approval and the same shall be communicated to Data Monitoring Committee and Clinical Trial Registry of India. The study will comply with the Declaration of Helsinki guidelines, local laws, and the International Council for Harmonisation - Good Clinical Practice (ICH-GCP) guidelines. After obtaining written informed consent from all study participants, the investigators will replace participant identifiers with unique research codes. Investigators will restrict access to research data by keeping the completed case report forms in a locked room and by using password-protected electronic files. All the research participants are insured, and any trial-related complications will be compensated for. Participants will be reimbursed for their travel expenses for follow-up visits.

Study settings

1. Department of Ophthalmology, Yenepoya Medical College Hospital, Yenepoya (Deemed to be) University, Mangalore, India.

2. Netrajyothi Charitable Trust Hospital, Udupi, India

Study period

September 2018 to September 2023.

Inclusion criteria

Patients aged >18 years with immature cataract attending the two study centres in Karnataka, India.

Exclusion criteria

History of significant ocular trauma, previous intraocular surgery, shallow anterior chamber (<2.5 mm), endothelial cell count <1500 cells/mm^2, pseudoexfoliation syndrome, previous/current intraocular inflammation (cells/flare/pigment over an anterior capsule or endothelium/posterior synechiae), preoperative fully dilated pupil <5 mm, and/or corneal endothelial dystrophy (presence of corneal guttae noted on slit lamp examination or specular microscope), and patients on oral tamsulosin or doxazosin. Cases with complications (posterior capsular rent, vitreous loss, zonular dialysis, nucleus drop, suprachoroidal haemorrhage, Descemet's membrane stripping intraoperatively, and postoperative endophthalmitis) will also be excluded from the analysis, but the rates of any post-randomisation exclusion events will be recorded and reported for per protocol analysis. Intention-to-treat analysis will also be done without any post-randomisation exclusions. However, complications that occur before the intervention, leading to conversion to manual small incision cataract surgery, will be excluded from the analysis.

Randomisation and masking

SK/CAG will approach potentially eligible participants attending the outpatient departments of the study hospitals. A research assistant at the study site will provide detailed information about the trial and obtain written informed consent. SK/ CAG will enrol the consenting participants after screening for exclusion criteria. SS will generate a random number sequence using a computer, which will be stored in secured envelopes. Central randomisation with stratified blocks of variable size will be used. Stratification will be done according to the Lens Opacities Classification System (LOCS) III grading of the cataract into two strata (Strata 1: Grade 1, 2 and Strata 2: Grade 3, 4)[34]. On the day of surgery, SK/CAG will contact the central randomisation unit and SS will allocate the participants into either of the two groups, i.e., bevel-up or bevel-down (Figure 1). SS will not be in direct contact with the participants. The trial participant, outcome assessor, and statistician will be masked. Theparticipant will not be aware of the group to which they were randomised and will not be able to differentiate the interventions. The outcome will be assessed by a trained research assistant who is unaware of the intervention. An independent statistician, who is unaware of the random allocation, willanalyse the data.

COVID-19 impact: Based on the ethics committee's recommendation to uphold participants' safety, we temporarily stopped the trial recruitment from March to June 2020 because of the COVID-19 pandemic. After restarting the trial, to increase the participant recruitment, we increased the number of investigators (surgeons) to five (three in one and two in another site), which the ethics committees approved. We would implement all the COVID-19 precautions during the trial. Both the research assistants are trained regarding COVID-19 precautions and vaccinated with the COVID-19 vaccine.

Interventions

Figure 2 shows the steps of the surgery. All surgeries will be performed under the peribulbar block. The bevel of the phaco tip will be held facing up during nucleus management in patients randomised to the "bevel-up group" and down in the "bevel-down group". Even if the surgeon, tilts the probe momentarily to engage the fragment, they will emulsify the fragment only in the assigned position (bevel-up or bevel-down). A surgeon outside the trial, masked to random allocation, will independently evaluate the video excerpts of a sample of the surgeries and assign them to bevel-up or -down groups, which will be compared to the original assignment. Balanced salt solution (BSS; Intasol, Intas pharma) with 1:1000 adrenaline (0.5 ml in 500 ml of BSS) (Epitrate, Sunways) will be used. Intracameral lignocaine, phenylephrine, or pilocarpine will not be used.

All surgeries will be performed by a three surgeons in site one and two surgeons in another site. To familiarise surgeons with the techniques, each surgeon will perform at least 25 surgeries using each technique before the start of the

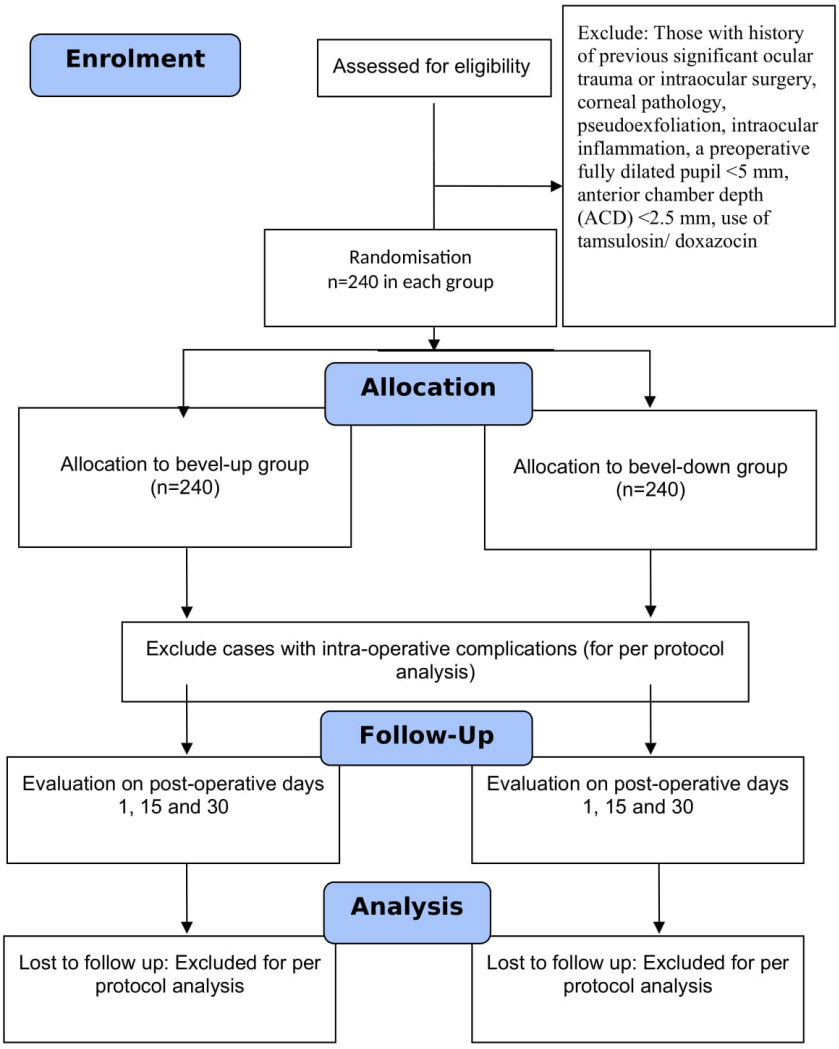

Figure 1. Proposed flow of participants in this trial.

trial. No strategies to improve adherence to intervention is required as it is a one-time procedure.

Phaco platform and parameters

We will use the Sovereign compact phacoemulsification system with WhiteStar technology and Ellips (Abbott Medical Optics, Abbott Laboratories, Abbott Park, Illinois, USA) for all the surgeries. Following are the parameters for the direct chop: maximum aspiration flow rate: 32 cc/min; maximum vacuum: 300 to 410 mm Hg; threshold vacuum: 170 mm Hg; and maximum power: 40 linear long pulse 8/12 (40%) with Whitestar on and occluded: 40 linear short pulse 6/12 (33%) with Whitestar on. A 19-gauge, 30-degree phaco tip will be used for all surgeries.

Preoperative evaluation

Preoperative evaluation includes uncorrected and corrected distance visual acuity (UDVA and CDVA), slit-lamp examination, applanation tonometry, an examination of retina with a non-contact 78 dioptre lens, and indirect ophthalmoscopy. Maximum pupillary dilatation will be noted 20 minutes after instillation of tropicamide with phenylephrine eye drops. The axial length (AL) and anterior chamber depth will be measured using an ultrasonic A-scan (Echorule Pro, Biomedix Optotechnik & Devices, Bangalore, India) or optical biometer (IOL Master 500, Carl Zeiss). CCT will be measured using an ultrasound pachymeter (Pacscan 300P, Ver 3 Rev U, Sonomed Escalon, Lake Success, NY) with an SD ≤0.09, with the patient fixating on a distant target. Endothelial cell density will be measured using specular microscope SP-1P (Topcon Europe Medical BV, Netherlands). Based on the nucleus colour, we will clinically estimate the hardness and grade according to LOCS III[34].

Intraoperative evaluation

We will note the mean phaco power (%), ultrasound time (UST), effective phaco time (EPT) (seconds) and the amount of irrigating fluid used.

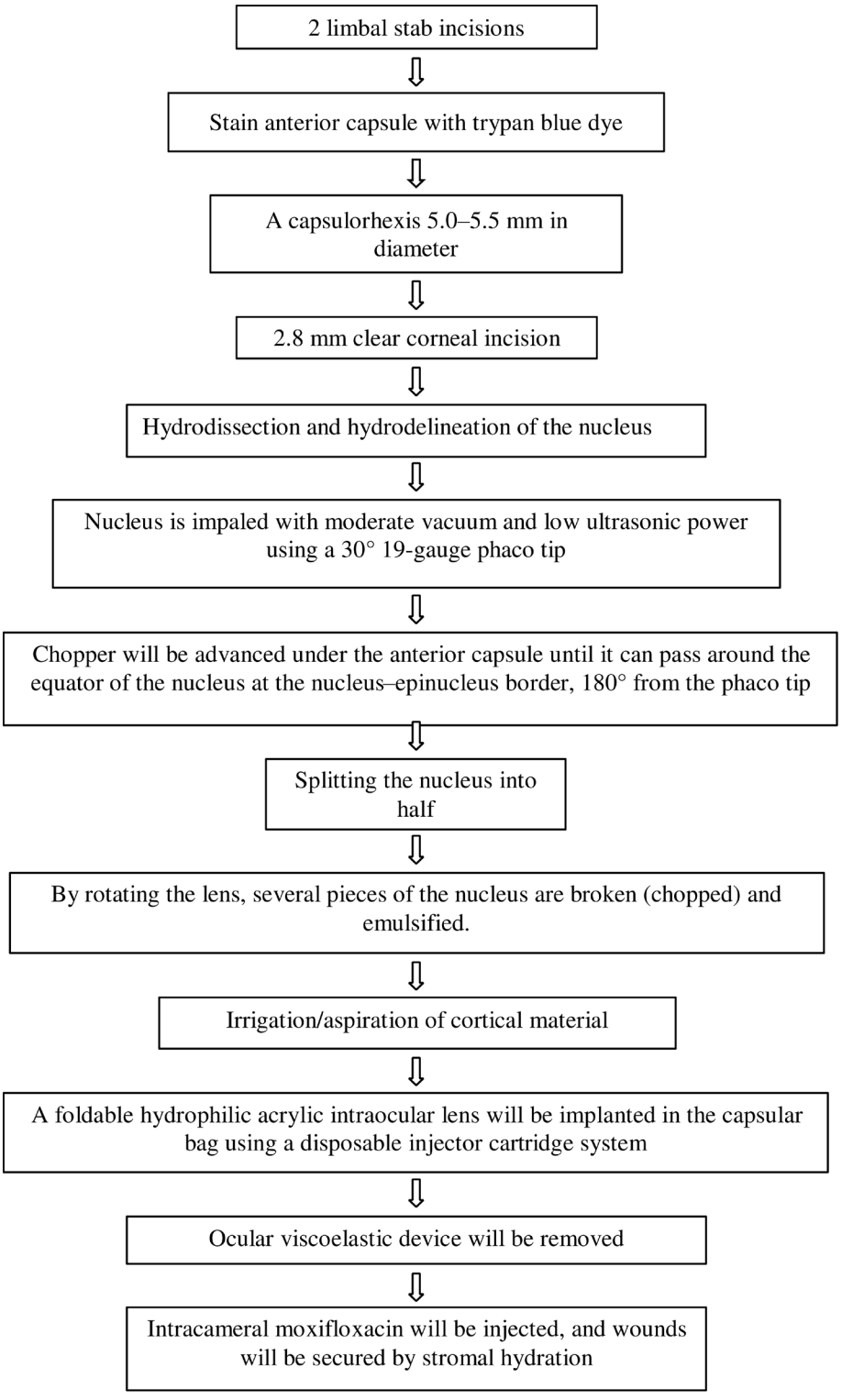

Figure 2. Surgical procedure.

Postoperative treatment

A combination of topical moxifloxacin and dexamethasone eye drops, one drop six times a day for the first week and gradually tapered over one month, will be administered.

Postoperative evaluation

The following examinations will be done on day 1, day 15 and at the end of one month: UDVA, CDVA, slit lamp biomicroscopy, applanation tonometry, fundoscopy and CCT

measurement. The endothelial count will be assessed at the end of one month. The coefficient of variation of cell size and percentage of hexagonal cells will also be measured. Automatic focusing and digital image capture will be used. In the case of a blurred and noisy image, the cells will be identified manually. The approximate centre of the cell will be marked using a stylus pen on the captured specular digital image. The guidelines for the use of the specular microscope in clinical trials as proposed by McCarey *et al.* will be followed[35]. Endothelial cell evaluation will be done through the same specular microscope throughout the study period at each site. The mean absolute reduction in the endothelial cells will be measured in both groups. The percentage of endothelial cell loss will also be calculated as = (preoperative cell count − postoperative cell count)/(preoperative cell count × 100%). Regular follow-up visits of the patients will be encouraged through telephonic reminders.

Outcome measures
Primary outcome: Endothelial cell count at one month postoperatively.

Secondary outcome: CCT on days 1, 15, and 30. Intraoperative complications will also be noted.

Sample size calculation
Based on a pooled standard deviation of 441.7, this study would require a sample size of 215 for each group to achieve a power of 90% and a level of significance of 5% (two-sided), for detecting a true difference of 138 cells/mm^2 (2516 - 2378) in the means between the study groups[26,36]. Expecting 10% attrition in this trial, we would recruit 240 eligible participants in each group (total 480).

Data collection and statistical analysis
Research assistants will collect all the relevant data on a case report form (CRF). Research assistants at each study site will independently enter the data from CRF into a password protected server. SK will regularly perform source data verification. We will follow double data entry method to identify data entry errors. In case of any discrepancy, the data query would be sent to the research assistant at the trial site to re-check the source data and inform the changes, if any. Any changes made in the CRF will be signed and dated to have an audit track.

A blind review of the data will be performed. The analysis will follow the intention-to-treat principle. 'Per protocol' analysis will also be performed excluding patients who experience intraoperative and postoperative complications, as the complications themselves can have a direct impact on the endothelial count. Descriptive statistics will be used to express the results. We will compare the mean endothelial cell counts between the study groups by bi-variate analysis. To assess the CCT difference between the study groups, repeated measures analysis of variance will be used. We will use Stata 17 software (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC.) for analysis.

Data monitoring
A data monitoring committee (DMC) with independent members is constituted (see *Extended data*)[37]. Based on their findings, the DMC will recommend continuation, modification or discontinuation, of the trial, with reports to the ethics committees.

Investigators will report any serious adverse events to the DMC and ethics committee within 24 hours. We will also enlist all the adverse events and report using descriptive statistics. We will compare the adverse events between the study groups.

Dissemination
The authors will present the results of the trial in conferences and publish them in relevant journals. All the de-identified data will be uploaded in an online repository at the end of the trial.

Study status
The trial is in the recruitment phase.

Discussion
Corneal endothelial cells are precious as they do not regenerate, and they only decrease with age. Although endothelial damage of varying degrees is known to occur in all intraocular procedures, techniques that minimise the endothelial damage should be favoured. Hence, ophthalmologists are continually striving to find a more cornea friendly technique of cataract surgery. Endothelial cell loss is of utmost importance in corneas predisposed to bullous keratopathy (such as those with Fuchs endothelial dystrophy) or in eyes likely to have more serious endothelial cell damage (e.g., those with a hard nucleus, old age, small pupil, and shallow anterior chamber)[13,16,38].

The quantum of corneal endothelial loss during phacoemulsification seems to be mainly determined by the heat generated at the phaco tip, cavitation energy, and the amount of ultrasound used[22–24]. The phaco tip position is likely to determine the impact of these factors on the corneal endothelium. Hence, it would be worthwhile exploring the phaco tip position (bevel-up or bevel-down) during phacoemulsification resulting in minimum corneal endothelial cell loss.

In a trial of 60 patients by Faramarzi *et al.*, the mean (SD) corneal endothelial cell loss was significantly lower (p=0.017) in the bevel-up group (156 ± 150) when compared to the bevel-down group (332 ± 363). On the contrary, Raskin *at el.* (n=25 in each group) reported that postoperative mean (SD) endothelial cell count was significantly more (p=0.02) in the bevel-down (2252 ± 310) when compared to bevel-up group (2393 ± 321). Based on the sample size and actual observed difference between the study groups, the powers of the studies were 69% and 36% for Faramarzi *et al.* and Raskin *et al.*, respectively[39]. Hence, neither of these studies had enough patients to detect whether a significant difference truly exists between the study groups. Moreover, potential confounders such as cataract grade and masking

were not explicitly addressed during randomisation or analysis.

A clinical trial can give rise to erroneous results through the introduction of bias/systematic errors, confounding (which can be restricted by randomisation) and random error (which can be minimised by using a large sample size)[40]. Keeping in view the limitations of the previous trials[22,25,26], we have adopted a robust design (stratified randomisation based on the cataract grade and triple-masking) with adequate sample size to detect the expected difference in the endothelial cell loss between the two groups. Additionally, this trial utilises specular microscopy, which is a fairly objective and non-invasive method of measuring the corneal endothelial cell count and morphology[41].

Conclusion

The proposed trial results will guide ophthalmic surgeons in choosing the most cornea friendly phaco tip position during phacoemulsification and subsequently minimise the incidence of iatrogenic bullous keratopathy.

Data availability

Underlying data

No underlying data are associated with this article.

Extended data

Open Science Framework: Does the phaco-TIp position during clear corneal Phacoemulsification Surgery adversely affect corneal endothelium? TIPS study protocol for a randomised, triple-masked, parallel-group trial of bevel-up versus bevel-down phacoemulsification. https://doi.org/10.17605/OSF.IO/5YS6W[37]

This project contains the following extended data:

- DMC charter.docx (Data Monitoring Committee charter)
- Informed consent form.docx (informed consent form in English)
- Netra jothi kannada consent 27.5.2019.pdf (informed consent form in Kannada)
- Malayalum consent 27.5.2019.pdf (informed consent form in Malayalum)

Reporting guidelines

Open Science Framework: SPIRIT and TIDieR checklists for "Does the phaco-TIp position during clear corneal Phacoemulsification Surgery adversely affect corneal endothelium? TIPS study protocol for a randomised, triple-masked, parallel-group trial of bevel-up versus bevel-down phacoemulsification" https://doi.org/10.17605/OSF.IO/5YS6W[37]

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Open Peer Review

Current Peer Review Status: ? ✓

Version 2

Reviewer Report 27 February 2023

https://doi.org/10.21956/wellcomeopenres.20845.r54509

✓ **Anthony Vipin Das**
Department of EyeSmart EMR & AEye, Kallam Anji Reddy Campus, LV Prasad Eye Institute, Hyderabad, Telangana, India

Thank you for addressing the comments provided in the earlier review.

I have no further comments on this version.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Cataract Surgery, Big Data, Ophthalmology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 21 June 2022

https://doi.org/10.21956/wellcomeopenres.17667.r50887

? **Anthony Vipin Das**
Department of EyeSmart EMR & AEye, Kallam Anji Reddy Campus, LV Prasad Eye Institute, Hyderabad, Telangana, India

Thank you for the opportunity to review this study protocol. Please find my observations below.

1. The authors present a robust study design to determine the ideal position of the phaco tip during phacoemulsification. The following two factors must be taken into consideration which are unique for each eye on the table.

2. While the ACD is being determined during the AScan, the actual ACD during the Phacoemulsification is dynamic based on the fluid dynamics in the Anterior Chamber. It is quite high in High Myopes and can be low in patients with occludable angles. In spite of this, there is variability in the ACD that can occur even in seemingly normal eyes. This is a judgement of the operating surgeon and must be considered as the space that is available for the phaco to be performed will vary accordingly.

3. The other aspect of the distance of the phaco probe from the endothelium is dependent on the plane of the probe during the procedure. The surgeon, if possible, must always maintain it at a constant depth, notably at the plane of the Iris. This will ensure that during the Quad mode of the Phaco Machine, there is a constant plane that is achieved to emulsify the fragments in the anterior chamber.

4. There is still a possibility for the probe to changes its plane as it aspirates the nuclear fragments, but the surgeon variance should be taken care of by two surgeons who will ensure that the major step of quadrant removal through the application of the phaco is performed in a standard plane of the iris, which is away from the endothelium.

5. Another aspect that must be taken into consideration is the LOCS grading of the cataract. While the nuclear sclerosis is determined pre-operatively. The amount of energy that might be required for aspirating the epinucleus and cortex must be judged by the operating surgeon. This is unique to each case and surgeon style on how much of aspiration is used by the probe and when the phaco is applied for the fragments that are harder.

6. It would also help to decide the standard number of fragments that the surgeon is planning to divide the nucleus into. Is it 4 or 6 or sometimes the phaco can be performed in just the 2 fragments in direct chop if they are soft enough and prolapse into the AC. This might help reduce the variance in the surgeon operating style.

7. The authors might also want to consider one of the most important factor for the health of the endothelium which is the irrigating solution. In reality, the use of BSS is expensive and not wide spread. They must also factor this in the study of the more commoner irrigating solutions used in the field by various surgeons in different ophthalmic practices.

8. The viscoelastic coating of the endothelium before the start of the phacoemulsification is also an important step in protecting the endothelium from the heat generated in the anterior chamber. Is this effect going to be also factored in on the type of viscoelastic used and also the quality of the product. If so, this step must be mentioned in the protocol whether it is being performed.

9. The corneal edema that ensues post the cataract surgery must also be factored in on first post-operative day. This also will indicate the insult caused to the endothelium during the surgery. There must be a standard way to grade the corneal edema on POP Day 1 and then

follow up on subsequent visits of resolution of the same. This will also guide on the time taken to resolution of the corneal edema and correlate with the final endothelial count at one month.

10. To engage the fragment, in certain instances a side bevel is used to engage the piece in a more predictable manner. Once the piece is engaged and away from the PC and endothelium, the phaco is applied to emulsify. In such instances, it would be interesting to understand what position the probe will be in while the quad step is being performed.

Please reflect on the above points which might add value to the study design and can incorporate accordingly. Thank you.

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Cataract Surgery, Big Data, Ophthalmology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 26 Dec 2022

Soujanya Kaup, Yenepoya Medical College Hospital, Yenepoya Deemed to be University, Mangalore, India

2. While the ACD is being determined during the AScan, the actual ACD during the Phacoemulsification is dynamic based on the fluid dynamics in the Anterior Chamber. It is quite high in High Myopes and can be low in patients with occludable angles. In spite of this, there is variability in the ACD that can occur even in seemingly normal eyes. This is a judgement of the operating surgeon and must be considered as the space that is available for the phaco to be performed will vary accordingly.
Response: We agree with your comments. We cannot quantify the intra-operative ACD variations. We presume that this variation will have occurred randomly in both the trial arms in a similar fashion. There are numerous factors that can affect EC loss during phacoemulsification. We are only trying to see the isolated effect of changing the tip

position on EC loss. We are presuming that stratified randomisation (with variable block size) will ensure balancing all known and unknown factors equally among both the trial arms. We have measured ACD pre-operatively and excluded those cases who have ACD of less than 2.5mm which is a known risk factor for increased EC loss.

3. The other aspect of the distance of the phaco probe from the endothelium is dependent on the plane of the probe during the procedure. The surgeon, if possible, must always maintain it at a constant depth, notably at the plane of the Iris. This will ensure that during the Quad mode of the Phaco Machine, there is a constant plane that is achieved to emulsify the fragments in the anterior chamber.
Response: There is still a possibility for the probe to changes its plane as it aspirates the nuclear fragments, but the surgeon variance should be taken care of by two surgeons who will ensure that the major step of quadrant removal through the application of the phaco is performed in a standard plane of the iris, which is away from the endothelium. All surgeries will be performed in the capsular bag. The surgeons are familiar with the standard surgical protocol and have been trained to follow the procedure as per the standard surgical protocol.

5. Another aspect that must be taken into consideration is the LOCS grading of the cataract. While the nuclear sclerosis is determined pre-operatively. The amount of energy that might be required for aspirating the epinucleus and cortex must be judged by the operating surgeon. This is unique to each case and surgeon style on how much of aspiration is used by the probe and when the phaco is applied for the fragments that are harder.
Response: It is probably reasonable for us to assume that the phaco energy is largely employed in nucleus removal rather than epinucleus. However, we will note the total amount of ultrasound energy used at the end of each surgery and compare this between the trial arms.

6. It would also help to decide the standard number of fragments that the surgeon is planning to divide the nucleus into. Is it 4 or 6 or sometimes the phaco can be performed in just the 2 fragments in direct chop if they are soft enough and prolapse into the AC. This might help reduce the variance in the surgeon operating style.
Response: I guess this could be observed retrospectively perhaps, rather than dictating it prospectively, but ideally it would be the same in each arm. The more energy that comes from the chopper, the less comes from the phaco probe, so it would be of potential significance if the surgeon were chopping up into 6 parts for bevel up, but only 2 parts for bevel down. However, as we will be noting and comparing the ultrasound energy used in both the trial arms we will know if we are using more phaco-energy in one group over the other.

7. The authors might also want to consider one of the most important factor for the health of the endothelium which is the irrigating solution. In reality, the use of BSS is expensive and not wide spread. They must also factor this in the study of the more commoner irrigating solutions used in the field by various surgeons in different ophthalmic practices.
Response: For the purpose of standardisation, we have used only one type of irrigating fluid. We are not trying to assess the factors contributing towards EC loss. We are only trying to see the isolated effect of phaco-tip position on EC loss keeping all other known

(and possible unknown) factors constant.

8. The viscoelastic coating of the endothelium before the start of the phacoemulsification is also an important step in protecting the endothelium from the heat generated in the anterior chamber. Is this effect going to be also factored in on the type of viscoelastic used and also the quality of the product. If so, this step must be mentioned in the protocol whether it is being performed.
Response: We will be using hydroxy propyl methyl cellulose to coat the endothelium uniformly across the trial arms.

9. The corneal edema that ensues post the cataract surgery must also be factored in on first post-operative day. This also will indicate the insult caused to the endothelium during the surgery. There must be a standard way to grade the corneal edema on POP Day 1 and then follow up on subsequent visits of resolution of the same. This will also guide on the time taken to resolution of the corneal edema and correlate with the final endothelial count at one month. **Response:** We will be assessing the central corneal thickness with pachymetry that will help us in assessing the corneal oedema post-operatively.

10. To engage the fragment, in certain instances a side bevel is used to engage the piece in a more predictable manner. Once the piece is engaged and away from the PC and endothelium, the phaco is applied to emulsify. In such instances, it would be interesting to understand what position the probe will be in while the quad step is being performed.
Response: For the purpose of the trial, we have standardised the surgical protocol to be followed. For all the surgeries under bevel-up group, the probe will be positioned in bevel-up position throughout the procedure and vice versa for bevel-down group. Even if the surgeon, tilts the probe momentarily to engage the fragment, they will emulsify the fragment only in the assigned position (bevel-up or bevel-down). This will be verifiable from the video excerpts which will be viewed by an external surgeon, masked to allocation, who will confirm which technique was being utilised. This now updated in the protocol.

Competing Interests: No competing interests were disclosed.

Reviewer Report 01 February 2021

https://doi.org/10.21956/wellcomeopenres.17667.r42165

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Peter A Mattei
Department of Medicine and Science of Ageing, Ophthalmology Clinic, University G. D'Annunzio Chieti-Pescara, Chieti, Italy

The trial design describes a randomised, multicentre (two centres with on surgeon per centre),

parallel-group, triple-masked (participant, outcome assessor, and statistician) trial with 1:1 allocation ratio of 480 patients (240 per phacoemulsification technique: bevel-up vs. bevel-down) to evaluate the endothelial cell count at one month postoperatively (primary outcome) and CCT on days 1, 15, and 30 (secondary outcomes).
My primary concerns are:

1. Lack of controls to determine if the bevel-up vs. bevel-down technique was followed as per allocation.

2. What percentage (time or energy) of the phacoemulsification must be done with the tip in this position. This aspect will probably affect the sample size calculation, as would the inclusion of confounding parameters such as centre/surgeon and grading strata.

3. The follow-up time would probably not be long enough to see the final endothelial cell loss or decrease in central thickness. see for example DOI: 10.1007/s10792-016-0283-7

4. I was unable to locate the data-set, maybe my fault.

5. How will the endothelial cell loss be recorded, absolute loss or percentage decrease, for the evaluation of between technique differences?

6. SPSS 16 is a bit outdated. Consider using R?

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Partly

Are sufficient details of the methods provided to allow replication by others?
No

Are the datasets clearly presented in a useable and accessible format?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: cataract surgery, statistical analysis

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 26 Dec 2022

Soujanya Kaup, Yenepoya Medical College Hospital, Yenepoya Deemed to be University, Mangalore, India

1. Lack of controls to determine if the bevel-up vs. bevel-down technique was followed as per allocation.
Response: The surgeons are experienced in cataract surgeries and were familiar with both bevel-up and bevel-down phaco phacoemulsification. Immediately prior to starting the trial, the surgeons were asked to perform a minimum of 25 cases with each technique so that they adhere to the standard operating procedure for the surgical protocols in each of the trial arm. At the end of each surgery, research assistant asks the surgeon to self-evaluate if they had any difficulty in adhering to the surgical protocol. If the surgeon states that they had to deviate from the surgical protocol, this would be noted and reported. Also, a randomly selected sample of the surgical videos will be independently evaluated by a surgeon outside the trial and will be asked to assign them to bevel-up or -down groups and this will be compared to the original assignment. This is updated in the procotol.

2. What percentage (time or energy) of the phacoemulsification must be done with the tip in this position. This aspect will probably affect the sample size calculation, as would the inclusion of confounding parameters such as centre/surgeon and grading strata.
Response: The phaco-tip will be placed in the given position (based on the randomisation) throughout nucleus management (i.e., 100% of the time). Assuming the randomisation was effective in distributing cataract density between the two arms, this is not a concern – and we therefore don't think it is necessary to use phaco time or energy as the driver for sample size calculation as the unit of randomisation is the patient not the "second of phaco time" or the "Watts of phaco power".

3. The follow-up time would probably not be long enough to see the final endothelial cell loss or decrease in central thickness. see for example DOI: 10.1007/s10792-016-0283-7
Response: It can be acknowledged that the graph of CCT post phaco may not reach total stability until a later time point (60 or 90 days in the study quoted). However, we think it is reasonable to assume that the endothelial cell counts and CCT at earlier time points are extremely strong predictors for final outcomes. We see no reason to be concerned that bevel up, or bevel down, might cause a late drop in cell count 3 months after surgery compared to the other arm of the trial. Also, studies have concluded that the rate of endothelial cell loss is maximum during the first month post-uneventful cataract surgery, and thereafter no accelerated cell loss takes place. Hence, we opted to choose post-op one month to evaluate endothelial count.

- Beato JN, Esteves-Leandro J, Reis D, Falcão M, Rosas V, Carneiro Â, et al. Corneal structure and endothelial morphological changes after uneventful phacoemulsification in type 2 diabetic and nondiabetic patients. Arq Bras Oftalmol;84(5):454–61. Available from: http://www.ncbi.nlm.nih.gov/pubmed/34586219

4. I was unable to locate the data-set, maybe my fault.
Response: There are no data-sets associated with this article. The DSMC Charter, Participant information sheet and Consent forms are available at https://doi.org/10.17605/OSF.IO/5YS6W

5. How will the endothelial cell loss be recorded, absolute loss or percentage decrease, for the evaluation of between technique differences?
Response: Both ways of presenting the data are possible. Absolute number of endothelial

cells lost will be measured in both the groups. Percentage of endothelial cell loss will also be calculated as = (preoperative cell count − postoperative cell count)/(preoperative cell count × 100%) Updated in the protocol.

6. SPSS 16 is a bit outdated. Consider using R?
Response: STATA 17 will be used. Updated in the protocol.

Competing Interests: No competing interests were disclosed.