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An exploratory randomised controlled clinical trial comparing a multifocal toric intraocular lens with standard multifocal lens plus incisional astigmatic surgery in patients undergoing bilateral cataract surgery

Version 1.2

Study Protocol

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Study Synopsis

Title	Toric Multifocal intraocular lens Vs non toric multifocal lens combined with incisional astigmatic surgery in patients undergoing bilateral cataract surgery.
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Background

Spectacle independence is a central aim in modern cataract surgery. Although bilateral monofocal IOL implantation, aiming for emmetropia or low myopia, leads to high levels of patient satisfaction in distance vision, spectacle dependence for reading and other near vision tasks is the usual result. One technique available to surgeons to reduce spectacle dependence is to use multifocal IOL. With increasing demands for complete spectacles independence from patients after cataract surgery, multifocal IOLs have been introduced widely in cataract surgery. This should result in less spectacle dependence for patients.

Residual astigmatism after cataract surgery can influence the post operative outcome of multifocal IOLs and lead to to poor visual performance of the multifocal lenses. Hence it is important to correct the astigmatism during cataract surgery to get the optimal result with Multifocal IOLs. Currently patients with high degrees of corneal astigmatism are denied multifocal lenses and in patients with low degrees of corneal astigmatism the option offered is attempting to correct the corneal astigmatism with corneal incisional surgery such as limbal relaxing incisions.

Combining a multifocal optic with a toric optic that corrects corneal astigmatism, so called multifocal toric lenses would correct the corneal astigmatism more precisely and therefore make the patient as much as possible spectacle independent. Results with toric IOLs (without a multifocal component) have achieved very good astigmatic control. Precise alignment of the cylindrical axis of the IOL with the astigmatic axis of the cornea is key for success.

The alternative method to reduce corneal astigmatism as part of cataract surgery is to make relaxing incisions (cuts) on the steeper axis of the cornea. This technique is in use since more than 2 decades and is widely used in clinical routine. As with toric IOLs, precise alignment of the cuts with the axis of astigmatism is essential. The disadvantage of the incisional techniques is the variability of the effect between patients since it depends on factors such as the extent of scarring of the cuts after surgery as well as corneal thickness and shape. Also, there may be a tendency for regression of the effect during the first 9 months after surgery. Furthermore there is a small risk of infection of the corneal incision and microbial keratitis after limbal relaxing incision has been described. The main advantage is the low cost.

Study objectives	Purpose of the present study is to compare the outcome of multifocal toric intraocular lens with standard multifocal lens plus incisional surgery in patients undergoing bilateral cataract surgery
Study design	Randomised controlled trial with intra-patient comparison
Study population	60 eyes (30 patients) with cataract and corneal astigmatism of 1.00 to 2.50 D
Investigational Product (Medical Device)	First eye to be operated: Multifocal toric IOL (Rayner, UK), or LRI with 600µm knife according to the Donnenfeld nomogram + Multifocal IOL (Rayner, UK). The contralateral eye will receive the alternative treatment
Main outcome variables	• Composite scoring of unaided distance and near vision (monocularly) • Residual astigmatism evaluation by Subjective Refraction and autorefraction (Topcon) • Any intraoperative or postoperative complications
Additional outcome variables	Simulated K-readings using corneal topography (Pentacam) Rotational stability of the IOL - angle of axis as measured from retroillumination photographs: Orientation [degrees] • Dysphototpsia and satisfaction/ questionnaire - monocularly • Reading speed Salzburg reading test - monocularly • Glare testing – monocularly(Oqas)

1 Introduction

1.1 Background

Spectacle independence is a central aim in modern cataract surgery. Although bilateral monofocal IOL implantation, aiming for 0.00 to -0.50D, leads to high levels of patient satisfaction, spectacle dependence for reading and other near vision tasks is the usual result. Most surgeons faced with a patient with bilateral cataract would leave them either emmetropic or with very low levels of post-operative myopia in both eyes. This leaves most patients dependant on spectacles for near visual tasks.

One technique available to surgeons to reduce spectacle dependence is to use a multifocal IOL. Recent diffractive IOL designs have improved spectacle independence while reducing the glare phenomena(1)(6). A European study of the Restor diffractive IOL found that 74.4% never wore spectacles, glare and haloes occurred in 8.5% and 4.2% of patients respectively and 95.7% of patients said that they would have the same implant again(2). Only one patient out of 127 had the IOL explanted because of glare and haloes. FDA data for the Restor reported a spectacle independence figure of 80% (www.fda.gov/cdrh/pdf4/p040020.html). Bilateral implantation with contemporary multifocal lens implants reduce spectacle dependence and is well tolerated; but it involves compromise for the quality of distance vision.

Residual astigmatism after cataract surgery can influence the post operative outcome and lead to poor performance of these lenses (3). Hence it is important to correct the astigmatism during cataract surgery to get the optimal result with Multifocal IOLs. The options available to correct astigmatism is either to implant a multifocal toric IOL or make limbal relaxing incisions combined with a multifocal IOL.

With increasing demands of patients concerning refractive outcome after cataract surgery, toric IOLs that correct corneal astigmatism have been introduced more widely to cataract surgery. Originally toric IOLs were used mainly for patients with high degrees of astigmatism, especially after corneal surgical procedures such as penetrating keratoplasties. Recently, toric IOLs are available from numerous manufacturers to correct lower amounts of astigmatism which are much more prevalent. This should result in less spectacle dependence of patients due to the precise nature of the astigmatic correction (4).

The new multifocal toric lenses combine the separate optical features of a standard multifocal lens and the toric lens to provide a superior multifocal outcome with precise and sustainable toric correction.

The alternative method to reduce corneal astigmatism as part of cataract surgery is to make relaxing incisions (cuts) on the steeper axis of the cornea. This technique is in use since more than 2 decades

and is widely used in clinical routine(5). As with toric IOLs, precise alignment of the cuts with the axis of astigmatism is essential. Nomograms for these astigmatism correcting incisions are available depending on the extent and the orientation of astigmatism and the age of the patient. The disadvantage of the incisional techniques is the variability of the effect between patients since it depends on factors such as the extent of scarring of the cuts after surgery as well as corneal thickness and shape. Also, there is a tendency for regression of the effect during the first 9 months after surgery. Furthermore there is a risk of infection of the corneal incision and microbial keratitis after limbal relaxing incision has been described. The main advantage is only the low cost.

Concerning alignment, the axis is defined by either corneal keratometry or topography, or both. Misalignments may be caused intra- or postoperatively. Intraoperatively, misalignment may happen due to cyclotorsion of the eye in the lying position or due to local anaesthesia, and due to imprecision of positioning of the IOL in the bag or of placing the astigmatism correcting incisions on the cornea. These imprecisions can be dealt with by preoperative marking of the eye in the sitting position and use of meticulous positioning of the IOL or incisions during surgery.

A Rayner single-piece open-loop IOL made of hydrophilic acrylate was shown to have a good haptic memory and is thought to adhere to the capsule resulting in little to no rotation after surgery. A toric optic design has been added to this multifocal IOL design.
One of the front and back surfaces of the lens defines a toric surface for an astigmatic optical correction, and one of the front and back surfaces, which can be the same surface or the opposite surface, defines a multifocal surface for a presbyopic optical correction, to provide visual acuity for astigmatic presbyopes

There is currently a study being conducted at Moorfields Eye Hospital comparing monofocal lenses with LRI surgery versus toric monofocal lenses. However this does not compare with the current proposal as in multifocal IOL surgery astigmatism control is definitively more important than in monofocal IOL surgery. The presence of residual postoperative astigmatism after multifocal IOLs cataract surgery is not advisable and most of the companies making multifocal IOLs advise not to operate on patients with more than 2.00 diopters of astigmatism and advocate minimizing astigmatism by means of incisional corneal surgery at the time of the cataract surgery.
Residual post-operative astigmatism leads to poor performance of multifocal lenses. One reason is that multifocal IOLs do reduce significantly contrast sensitivity especially in some light condition and adding astigmatism does have a negative impact in further reducing contrast sensitivity. Furthermore, the presence of astigmatism makes the multifocal generated near , intermediate and distance images more blurred and thus makes the brain process of learning to focus on a given image for near, intermediate and distance much more difficult for the patient.

Toric multifocal IOLs are the latest multifocal IOLS generation and do have the huge potential of massively improve the outcome of multifocal IOL surgery hence the relevance of this exploratory study. Finally whilst a monofocal toric IOL does have only a toric surface the multifocal toric IOL does have a more complex construction incorporating the multifocal and toric surfaces on one single IOL and hence comparison in terms of astigmatism reduction between the monofocal and multifocal IOLs may not be meaningful since a new variability is introduced with the multifocal toric IOL.

We plan to compare the visual performance and outcome of the non toric multifocal IOL combined with corneal incisional surgery to correct astigmatism with a toric multifocal IOL alone.

1.2 Rationale

To assess the efficacy of multifocal IOL with corneal pre-existing astigmatism and compare the outcomes of a multifocal toric IOL or a standard multifocal IOL combined with limbal relaxing incisions.

1.3 Risk/benefit assessment

Safety: both IOL used are CE approved and toric monofocal is well estabilished already . One of the major problems of all studies with multifocal IOL is astigmatism correction. Hence the incorporation of toric component to the multifocal IOL should result in a better performance of the multifocal IOL in patients with corneal astigmatism.

The investigation will show whether multifocal toric IOLs are superior to corneal incisional surgery plus standard multifocal IOL that is readily used in clinical practise, in correcting astigmatism in patients with age-related cataract. This study will also show if correction of astigmatism with a toric mutifocal IOL leads to better visual performance of the multifocal IOL. Since the IOL design studied is well known and has a long track record in the non-toric variant, and the non-invasive measuring procedures in this study are well tolerated, the benefit/risk ratio is acceptable. The contra lateral eye will receive limbal relaxing incisions with the multifocal IOL in the non-toric form. Since only patients that have low to moderate astigmatism are included in the trial, the difference in outcome should be small enough to ensure that the postoperative difference in residual astigmatism is small enough to not compromise binocular vision.

2 Study objective

Purpose of the present study is to compare efficacy of multifocal IOL after correction of astigmatism with either implanting a multifocal toric IOL or implanting a standard multifocal IOL combined with limbal relaxing incisions.

3 Investigational plan

3.1 Design

Randomised controlled trial with intra-patient comparison (bilateral study)

3.2 Selection of study population

The participants will be selected by the clinical investigators

3.2.1 Number of subjects

60 eyes of 30 patients with bilateral cataract.

3.2.2 Pre-study screening

The following examination will be carried out in each patient before cataract surgery:

- A full ophthalmic examination including slit lamp biomicroscopy and retinal examination.

3.2.3 Inclusion criteria

- Bilateral cataract and be planning to have both eyes operated on.
- Age 21 and older
- Have cataracts that allow IOL master biometry
- Regular corneal astigmatism 1.00 up to 2.50 D
- Difference of corneal astigmatism in both eyes to be equal to or less than 0.75D
- written informed consent to surgery and participation in the study
- Speak English

3.2.4 Exclusion criteria

Any of the following will exclude a subject from the study:

- Relevant other ophthalmic diseases such as: pseudoexfoliation, glaucoma, traumatic cataract corneal scars, and other co-morbidity that could affect capsule bag stability (e.g. Marfan syndrome)

- Irregular corneal astigmatism on Pentacam topography

Surgery should be :

- Performed by consultants
- Second eye to be listed within 3-4 weeks whenever possible.

3.3 Investigational Product (Medical Device)

The investigator will dispense the investigational product only to subjects included in this study.
All IOL supplies will be stored in accordance with the manufacturers' instructions.
Details of the exact date of IOL implantation will be documented in the case report form.

3.3.1 Medical Device (IOL) used in the study

Toric Multifocal IOL (Rayner) – Model M-Flex T 588 or 638 - CE marked since January 2007
Non-toric Multifocal IOL (Rayner) – Model M-Flex 630F - CE marked since 2006 (in routine use)

3.4 Study protocol

The study will be performed at the Moorfields Cataract Centre, St. Ann's outreach, London.

3.4.1 Study Visits

On the day of pre-operative examination, the patient will undergo a full ophthalmic assessment and routine biometry is performed using the IOL Master by Zeiss for axial length measurement and K-readings. Additionally, a corneal topography (Pentacam) will be performed. The software for calculating the toric power is supplied by the manufacturer Rayner. The most appropriate of the available toric powers of the IOL will be used.

Surgery is performed under topical anaesthesia. Preoperatively, the horizontal meridian will be marked in the sitting position with a blue marking pen or insulin syringe at the limbus. The temporal self sealing incision, injection of viscoelastic substance, capsulorhexis, phacoemulsification, irrigation/aspiration of cortical material and injection of viscoelastic substance into the capsular bag are performed as standard procedure. According to randomisation, the multifocal toric IOL will implanted or corneal limbal relaxing incisions (LRI) according to the Donnenefeld nomogram will be performed combined with standard multifocal IOL.

The IOL is implanted via injector into the capsular bag. Following the implantation of the IOL, the toric axis is positioned in the planned axis by rotating the IOL. Then the viscoelastic

substance is aspirated thoroughly from the eye.

The LRI eye will receive a temporal or an on-axis incision with limbal relaxing incision with a 600µm single-use steel blade combined with a non-toric multifocal IOL. The location, length and site of LRIs will be made after calculation according to the Donnenfeld nomogram (www.lricalculator.com).

Extra trial visit

3-4 months after the second eye has been operated on.

Follow-up examinations are performed as depicted in the table:

Assessments/Examinations	Visit 0	Visit 1	Visit 2	Visit 3
	PreOp	Op day (after 1 hr)	1 month	3 months
Autorefractor	X		X	X
Subjective Refraction				X
Near, Distance VA			X	X
IOL Master Keratometry	X		X	X
Topography (Pentacam)	X		X	X
Retroillumination photo		X	X	X
Slitlamp examination	X	X	X	X
Dysphototpsia and satisfaction questionnaire				X
Reading speed(Salzburg reading test)				X
Contrast Vision(Pelli Robson chart)				X
Glare testing(oqas)				X

Postoperative standard medication: dexamethasone gtt, qid for 2 weeks and then bid for one week, chloramphenicol gtt qid for 2 weeks

3.4.2 Withdrawal and replacement of subjects

Subjects must be withdrawn under the following circumstances:

- at their own request

3.5 Variables and schedule of observations

3.5.1 Outcome variables

Main outcome variables

- Composite scoring of unaided distance and near vision (monocularly and binocularly)
- Residual astigmatism evaluation by Subjective Refraction and autorefraction (Topcon) and
- Any intraoperative or postoperative complications

Additional outcome variables

Simulated K-readings using corneal topography (Pentacam)

Rotational stability of the IOL - angle of axis as measured from retroillumination photographs: Orientation [degrees]

- Dysphototpsia and satisfaction questionnaire - monocularly
- Reading speed Salzburg reading test - monocularly
- Glare testing (Oqas)– monocularly
- Post-operative dominance will be established using the visual acuity results to ensure that there are equal numbers of dominant and non-dominant eyes in both groups

4 Methods of evaluation

4.1 Assessment of residual astigmatism

Measurement of residual astigmatism will be derived from autorefraction with an autorefractor (Topcon) with mean reading of 5 consecutive measurements in IOL mode, a subjective refraction by an optometrist using trial lenses and the cross cylinder method. All these measurements are non-invasive, non-contact and readily used in daily clinical practice.

4.2 Assessment of corneal astigmatism

Measurement of corneal astigmatism before and after surgery will be performed using the autokeratometry function of the IOL-Master (Zeiss) and the Scheimpflug technique

(Pentacam, Oculus). In the latter case, the simulated K-readings of the central 4 mm zone will be used.

4.3 Assessment of visual acuity

Measurement of uncorrected and best corrected visual acuity will be done using a back-lit EDTRS chart placed at 4m.
Near and distance unaided and corrected visual acuity will be measured

Reading speed, reading acuity and ciritical print size monocularly (Salzburg Reading Desk)
The Salzburg Reading Desk (SRD) is the prototype of a reading chart that measures reading speed and reading distance. Contrast and light conditions are preset and reading distance (+/- 0.2 cm), reading speed and their changes during the examination are measured. This ensures an objective evaluation of measurements under the same conditions at every follow-up.

Contrast vision under photopic and mesopic conditions (Pelli-Robson Chart)

Glare testing monocularly by Oqas:
The OQAS system consists of laser diagnostic sensory equipment, a computer workstation and custom designed software. It works by sending in an infrared light source and directly measuring the point spread function (PSF) of the optical system of the eye. Because OQAS measures all light reflected back off the retina, the measurement contains the effects of light scatter and all high order abrrations.

Dysphotopsia and satisfaction questionnaire – comparing the visual quality of the eyes as assessed under different conditions – to be filled in by patients at home shortly before the 3 months follow-up (see attachment)

4.4 Assessment of IOL position and rotation

IOL axis measurements are assessed from photos attained with a high-resolution digital retroillumination imaging system. The optical system consists of a Zeiss 120 slit-lamp for observation and imaging. A Zeiss retrolux illumination module is supplied with illumination provided by a Zeiss anterior segment flashpack through a fiber optic cable. For image acquisition we use a colour digital camera (Canon D5). The main advantage of this camera is the high light sensitivity of the large CCD chip, resulting in a high signal-to-noise ratio in the

acquired images. The images are directly transferred to a personal computer and saved to hard-disc. The images are assessed using a dedicated analysis software.

The axis marks are identified with a cursor and the axis of the IOL is registered. In order to ensure consistent alignment of the patient's head at each follow-up, the patient's head will be positioned as straight as possible according to the examiners subjective impression. A pilot

	A	B	C	D
	Excellent	Good	Average	Poor
Distance VA (log mar)	0.0 or better ie. 6/6 or better	<0.0 to 0.18 ie. 6/6 to 6/9	<0.18 to 0.30 ie. <6/9 to 6/12	<0.30 ie. <6/12
Near VA	N5 or better	<N5 toN6	<N6 to N8	<N 8

study has shown this to be reproducible to about 2° concerning axis documentation.

4.5 Data handling procedures

A case record form will be completed for each patient. The entries will be checked by trained personnel and any errors or inconsistencies will be checked immediately.

4.5.1 Data Management

All data will be entered into a specially designed ACCESS database by the Research Fellow. This database will be on the H drive of Moorfields Eye Hospital intranet and will be password protected and only accessible by authorised personnel.

4.6 Biometric methods

4.6.1 Biometric methods - outcome variables

The outcome variables will be assessed using descriptive statistics.

4.6.2 Biometric methods - Adverse events/Safety investigations

All adverse events will be properly listed and an appropriate method will be used to summarise the data.

4.7 Data Analysis and Use of study findings

We propose to generate a composite measure with 4 categories based on measures of distance and near visual acuity, but will use this pilot data (with patient questionnaire data) to determine how best to do this.

Components of the Visual Scoring System

The findings of this pilot study will be published by the investigators in a scientific journal and presented at scientific meetings, and will be used to power a full-scale randomised controlled trial.

4.8 Benefits and Risks

Patients will have the opportunity to take part in a project that offers them the chance to be spectacle independent. The risks to the patients above those of the surgery itself will come from intolerance of whichever treatment arm they are randomised to. These risks are low, The European study of diffractive IOLs found that 74.4% never wore spectacles, glare and haloes occurred in 8.5% and 4.2 % respectively and 95.7 % of patients said they would have the same implant again (2).

Where a patient is intolerant of the multifocal IOL they will be offered bilateral sequential IOL exchange with monofocal implants. Any further refractive surgery(7) required (e.g. residual bothersome astigmatism) will be performed if needed and after risks/benefit explanation and the costs will be met by the company sponsoring the trial (Rayner). In addition, Rayner Intraocular Lenses Ltd have agreed to supply all the lenses required for this trial free of charge and have agreed a small unrestricted grant of upto £5,000 to cover the costs of the study.

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