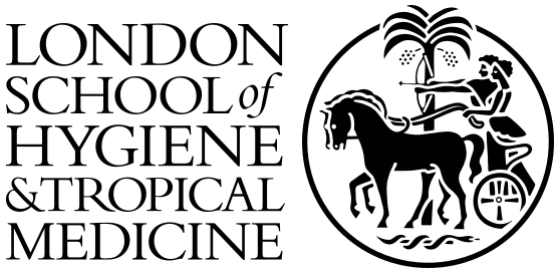

TITLE:

Phacoemulsification compared to phacotrabeculectomy surgery: a within-person observational cohort study.

SUB-TITLE:

A within-person observational cohort study comparing phacoemulsification with phacotrabeculectomy in fellow eyes of Tanzanian patients as therapy for concurrent cataract and primary open angle glaucoma.

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ABSTRACT

AIM: To compare reduction in intraocular pressure (IOP) and gain in visual acuity (VA) following phacotrabeculectomy (PT) and phacoemulsification(phaco) in Tanzanian patients with Primary Open Angle Glaucoma(POAG)

SETTING: CCBRT Hospital, Dar es Salaam, Tanzania

DESIGN: Within-person observational cohort study

METHODS: Within each patient, one eye had PT and the other phaco. Patients were followed for up to 5 ½ years and IOP and VA in each eye was assessed. For a small group of patients two additional post-operative time points were compared.

RESULTS: 52 patients (34 male) with a mean age of 70 years (SD 8 years), were enrolled in the study. For those with 250+ days follow-up, both operations resulted in lower IOPs and improved VA ($p<0.001$). The average drop in IOP was 50% (95%CI 45-55%) for PT and 41% (95% CI 36-46%) for phaco. Mean IOP was lower in the PT group 12.9mmHg vs 16.8mmHg ($p=0.004$). Extended follow-up in 9 patients showed a rise in IOP of 1.8mmHg for PT and 4.2mmHg for phaco eyes between first (mean 337 days) and second (mean 1482 days) follow-up ($p=0.18$).

CONCLUSION:. In this small study in African patients phacotrabeculectomy resulted in lower IOPs than phacoemulsification alone but the difference between the procedures was relatively small. Phacoemulsification alone was effective in reducing IOP and improving VA for several years in this population. Given the relative simplicity of phacoemulsification, it is a therapeutic option worthy of consideration in some settings.

(Words 236)

INTRODUCTION

More than 80% of the 285 million visually impaired individuals in the world live in low and middle income countries, with 15% in Africa despite this continent having only 12% of the world's population. [1.] Cataract and glaucoma are leading causes of blindness in Africa [2,3,4]. Since they are both age related conditions they often co-exist [5]. Both have surgical solutions, but debate continues with respect to the optimal management strategy. Trabeculectomy surgery for glaucoma is known to accelerate cataract[6]. After trabeculectomy the risk of requiring cataract surgery is reported as between 20% and 52% up to 7 years postoperatively. However, cataract removal after trabeculectomy surgery increases the risk of trabeculectomy failure which can range from 10-61% within 3 years of cataract surgery [6]. Many patients in Africa are financially constrained and live in rural areas, rendering two operations unaffordable or impractical.

We recently undertook a randomised controlled trial to evaluate the efficacy of intraoperative beta radiation compared with the standard 5 Fluorouracil as an adjuvant therapy in primary open angle glaucoma (POAG) in Tanzanian patients undergoing phacotrabeculectomy. The success rate in this phacotrabeculectomy trial (PTT), as measured by a continuing IOP reduction (IOP<16mmHg) at one year, was over 70%.

It has long been appreciated that cataract surgery alone lowers intraocular pressure [7, 8, 9.] There has been increasing debate as to whether cataract surgery alone may be an option for management of glaucoma in some circumstances. Table 1 summarises the recent published literature.

Table 1: Summary of literature comparing IOP reduction in Phacotrabeculectomy and Phacoemulsification surgeries

Ref No	Title/ Author	Type of study	No. of eyes & Preoperative IOP	Post-operative IOP	Follow up duration	Comments
10	Long term effects of phacoemulsification with IOL implant in normotensive and ocular hypertensive eyes. Poley B, Lindstorm R et al J Cataract Ref Surg 2008, 34:5 Pp 735-742	Retrospective review of case records in American patients	588 eyes 31-23mmHg 22-20mmHg	IOP reduction by 6.5mmHg (27%) 4.8mmHg (22%) in pre-surgical	1 year	IOP reduction was greatest in eyes with highest pre surgical IOP and at 1 year. IOP sustained over 10 years
11	Long term changes in IOP after clear corneal phacoemulsification : Normal patients versus glaucoma suspect and glaucoma patients. Shingleton B, Gamell L, O'Donoghue M et al J Cataract and Ref Surg 1999 25:7 885-890	Retrospective review of case records in American patients	164 eyes normotensive IOP 16±3 75 eyes glaucoma suspect IOP18±4 71 eyes glaucoma group IOP 17±5	 14±3 16±3 16±4	1 year	Reduction statistically significant in normotensive and glaucoma suspect groups.
12	Intraocular pressure reduction after phacoemulsification with intraocular lens implantation in glaucomatous and non-glaucomatous eyes: Evaluation of a causal relationship between the natural and open-angle glaucoma Poley B, Lindstrom	Retrospective review of case records in American glaucoma patients included, case mix of those on drops, had glaucoma surgery or both.	124 eyes, Preoperative IOP groups 29-23mmHg 22-20 19-18 17-15 14-5 All eyes	Final IOP change (%) -8.4±4.3 (34) -4.6±2.5 (22) -3.3±2.6(18) -1.1±2.2 (7) +1.9±3.6 (16) -2.7±4.3 (97)	1-10 years	Higher initial IOP results in greater IOP reduction

	R, Samuelson T et al J Cataract Refract Surg 2009; 35: 1946-1955					
13	Effect of cataract surgery on intraocular pressure control in glaucoma patients Hayashi K, Hayashi H, Nakao F, Hayashi F J Cataract Refract Surg 2001; 27:1779-1786	Prospective included both Angle Closure and open angle glaucoma in Japanese patients	ACG 74 patients Preoperative IOP 21±4 OAG 68 patients Preoperative IOP 21±5	 Postop IOP reduction 7.2±3.5 Post op reduction 5.3±4.8	24 months	IOP reduction more and effect lasts longer in ACG than POAG
14	Long-term effect of phacoemulsification on intraocular pressure using phakic fellow eye as control Chang T, Budenz D, Liu A, Kim W, et al J Cataract Refract Surg 2012; 38: 866-870	Retrospective review of case record in American patients Comparative between operated and phakic fellow eye	29 eyes Preoperative IOP 16±3 Fellow eye IOP 16±4	Postop IOP 14±2 Fellow eye IOP 15±3	36 months	No significant IOP lowering effect in operated eye compared to phakic fellow eye

Friedman D et al [15] did a systematic literature review to address the question of whether cataract surgery alone, combined cataract and glaucoma surgery or trabeculectomy surgery alone achieved better IOP control. They conclude:

- There are insufficient data to determine the impact of phacoemulsification surgery on short term (≤ 24 hours) IOP control
- Extra capsular cataract extraction (ECCE) surgery alone increases IOP in the short term
- There are insufficient data to determine whether short term IOP control is better with combined cataract and glaucoma surgery than with cataract surgery alone

- There is consistent evidence that cataract extraction alone decreases the IOP of glaucoma patients by, on average, 2-4mmHg at 1-2 years post operatively
- Combined phacotrabeculectomy reduces IOP by approximately 8mmHg at 1-2 years post operatively
- Combined ECCE trabeculectomy lowers IOP by 6-8mmHg at 1-2 years post operatively
- Longer term IOP control is better with combined glaucoma and cataract surgery than with cataract extraction alone.

A Cochrane review undertaken by Zhang ML et al [16] found only low quality evidence that combined cataract and glaucoma surgery may provide a small benefit in terms of IOP control compared to phacoemulsification. No studies comparing cataract surgery alone with combined phacotrabeculectomy have been reported from Africa.

If cataract surgery alone can reduce intraocular pressure low enough and maintain low pressure for a long time then this may represent a better option for elderly Tanzanian patients than combined cataract and glaucoma surgery. Moreover, early visual rehabilitation in such patients may not only encourage them to return for follow up should the need for trabeculectomy arise but also encourage other patients with similar conditions to attend eye clinics and undergo surgery. This study compares IOP and visual acuity after combined phacotrabeculectomy or phacoemulsification alone in eyes with both glaucoma and cataract.

METHODS

We undertook an observational cohort study taking advantage of the PTT, to compare IOP reduction and visual acuity improvement after phacotrabeculectomy and phacoemulsification surgeries. Details of the PTT are published elsewhere [17]. In summary patients with primary open angle glaucoma and cataract fulfilling the inclusion criteria (table 2) were recruited in the phacotrabeculectomy trial. For inclusion in this study both eyes had to satisfy these inclusion criteria.

Table 2: Referral, Inclusion and Exclusion criteria

Referral criteria	Inclusion criteria	Exclusion criteria
• IOP >21mmHg • C/D ratio >0.8 • Age > 40 years • Any form of cataract	• Characteristic glaucomatous changes in the optic disc. The presence of a focal or diffuse area of optic disc rim loss, so that the neuroretinal rim tissue in any quadrant is less than 5% of the disc diameter in that meridian. Extensive loss of neuroretinal rim tissue with marked optic disc cupping giving a cup disc ratio greater than 0.8. • A measured intraocular pressure greater than or equal to 21 mmHg on at least one visit before the time of listing for surgery as measured by Goldmann applanation tonometry. • An open angle on gonioscopy • Cataract sufficient to decreas vision and require surgical intervention.	• Unwillingness to participate in the study • Anterior segment neovascularisation • Past trauma to the eye or ocular adnexae • Retinal or optic nerve neovascularisation • Aphakia or pseudophakia • Previous ocular surgery • Uveitis • Inability/unwillingness to give informed consent • Unwillingness to accept randomization • Pregnancy or female of childbearing age who may be pregnant at the time of treatment (LMP) • Chronic use of topical or systemic steroids

Following informed written consent, patients with bilateral POAG and cataract were enrolled in the PTT. Each enrolled patient underwent phacotrabeculectomy on the eye with better visual acuity with random allocation to receive either adjunctive 5FU or beta radiation at the time of surgery [17]. In a number of patients enrolled in the trial, phacoemulsification with IOL implant alone was subsequently performed in the fellow eye. This report concerns those individuals who underwent phacotrabeculectomy in one eye and then phacoemulsification alone in the fellow eye. The primary outcome was IOP reduction from baseline. The secondary outcome was visual acuity change from baseline. In the PTT, patients were reviewed on day 1, and then after 1, 3, 6 and 12 months. At every visit unaided and pin hole visual acuity were measured using a reduced logarithm of minimum angle of resolution acuity chart (log MAR) by an optometrist who was trained to use the chart. The tumbling E chart (log MAR) was used for unlettered patients. Prior to phacoemulsification surgery baseline logMAR acuities were recorded. If follow-up acuities were Snellen these were converted to logMAR equivalents. For the purposes of analysis count fingers vision at 1 metre or less was recorded as 2.0, hand motions as 3.0, and perception of light as 4.0. The last review with the longest period of follow-up was taken. At a post-operative period of more than three years an attempt was made to review all patients again. Nine patients attended for review creating a second follow-up time point. Intraocular pressure was measured using a Goldmann tonometer which was calibrated and checked at the beginning of each clinic. For baseline IOP the median of three readings taken at different times of the day was taken. For follow-up of PTT the same outcome was used. For the phaco-only eyes a mean of two readings at separate times was used. Patients with increasing IOPs (>18) and/or glaucoma progression were started on appropriate anti-

glaucoma medication. Data were recorded on a pre tested case report form and entered using Excel. Data were analysed using Stata version 13 (www.stata.com). Paired t-tests were used to compare outcomes between eyes within individual patients. Where small numbers were present the non-parametric Wilcoxon matched-pairs signed-ranks test was used. P-values presented are 2-sided P-values.

Ethical clearance for this observational cohort study was granted by the CCBRT hospital ethical committee.

RESULTS

52 patients, 34 (65%) of whom were male, were enrolled in the study. In all patients the operation on the phacoemulsification only eye was undertaken after the phacotrabeculectomy eye. The phacoemulsification was undertaken a median of 125 days (first quartile 85, third quartile 233, range 26-902days) after the phactotrabeculectomy. Baseline characteristics of the study group are shown in table 3.

Table 3: Baseline characteristics of study population

Characteristic		N (%)
Gender	Male	34 (65%)
Age (years)	50-59	5 (10%)
	60-69	17 (33%)
	70-79	27 (52%)
	80-89	3 (6%)
Retired		20 (38%)
Education	None	20 (38%)
	Primary	19 (37%)
	Secondary	5 (10%)
	Tertiary	8 (15%)

Thirteen patients were taking topical medication prior to the surgery, in all instances this topical therapy had been taken for less than six months in total prior to the surgery. The mean

preoperative spherical equivalent refractive error was -1.9 (range +2.5 to -7.25). All patients had gonioscopy at presentation and had wide open angles. Mean age at phacotrabeculectomy surgery was 70 years (SD 8 years) and three quarters of patients were aged 65 years or more. Preoperative visual acuities, IOPs and CD ratios were comparable in both eyes (PT 0.68 vs P 0.78, PT 31.8 vs P 30.4 and PT 0.81 vs P 0.79). Seven patients were on topical treatment at the time of last review. None were listed for further surgery.

Final vs pre-operative IOP and VA

Restriction to those with 250 days or more follow-up in both eyes showed strong evidence (p=0.004) that both operations resulted in lower IOPs with an average 16.8mmHg or 50% (95%CI 45-55%) drop in IOP for phacotrabeculectomy and 12.9mmHg or 41% (95% CI 36-46%) drop for phaco alone. There was also evidence that both operations resulted in improved visual acuities in the region of 0.2 or more logMAR (P<0.001 for phacotrabeculectomy; P=0.03 for phacoemulsification).

Time periods of follow-up were paired for P and PT eyes for comparison. Nine individuals had two time periods with matched data.. Tables 4 and 5 show the IOP and VA findings by period of follow-up for 61 paired time points. The overall average period of follow-up in the phacotrabeculectomy group was 512 days and in the phacoemulsification group 485 days. Apart from the very early follow-up period, the reduction in IOP was consistently greater in the PT group. .

Table 4: Post-operative IOP outcomes for Phacotrabeculectomy and Phacoemulsification only eyes by 'paired' period of follow-up.

Mean ollow-up	N	Phacotrabeculectomy IOP (mmHg) Mean (SD)	Phaco IOP (mmHg) Mean (SD)	Paired ttest (Wilcoxon)	Mean IOP reduction Phacotrabeculectomy Mean (range, SD)	Mean IOP reduction Phaco mean (range, SD)	Paired t test (Wilcoxon)
<50 days	6	17.6 (SD 6.3)	15.0 (SD 1.8)	p= 0.46	13.8 (4 to 36, SD 11.5)	18.0 (9 to 32, SD 18.2)	p = 0.25
6 months (110-245 days)	14	14.5 (SD 6.5)	16.4 (SD 3.3)	p=0.15	16.2 (-1.5to26.5, SD 7.5)	13.6 (3to20, SD 5.5)	p=0.13
1 year (250-450 days)	26	14.6 (SD 4.7)	15.9 (SD 4.1)	p=0.91	18.8 (4to48, SD 10.0)	15.1 (1to42, SD 8.8)	p=0.02
2 years (475-885 days)	6	17 (SD 2.9)	19 (SD 7.1)	p= 0.92	13.7 (6to20, SD 6.0)	9.3 (-3to18, SD 7.5)	p= 0.46
3-5 years (1140-2022 days)	9	15.2 (SD 4.0)	19.8 (SD 4.7)	p=0.08	13.6 (3to25, SD 6.4)	9.5 (1to17, SD 4.6)	p= 0.15
250-2022 days	33*	15.6 (SD 4.4)	17.2 (SD 4.8)	p=0.06	16.8 (3to48, SD 10.0)	12.8 (-3to42, SD 8.4)	p=0.009

* The denominator is reduced here since those with more than one paired observation point were removed from the data and only the longest period of follow-up in each individual used for the analysis

Table 5: Post-operative logMAR visual acuity outcomes for Phacotrabeculectomy (PT) and Phacoemulsification (P) only eyes by 'paired' period of follow-up.

Mean follow-up	N	Phacotrabeculectomy logMAR change Mean (range, SD)	Phaco logMAR change Mean (range, SD)	Paired ttest (Wilcoxon)
<50 days	6	0.08 (-0.3 to 0.4, SD 0.25)	0.07 (-1.1 to 1.7, SD 0.90)	p= 0.83
110-245 days	14	0.15 (-1to0.5, SD 0.38)	0.14 (-1.2to0.6, SD 0.43)	p= 0.75
250-450 days	26	0.28 (-0.2to1.5, SD 0.34)	0.23 (-1.6to1.7, SD 0.73)	p= 0.37
475-885 days	6	0.32 (-0.3to1.5, SD 0.61)	0.21 (-0.1to0.50, SD 0.21)	p=0.35
1140-2022 days	9	0.13 (-0.8to0.6, SD 0.40)	-0.07 (-3.1to1.4, SD 1.28)	p=0.68
250-2022 days	33*	0.28 (-0.8to1.5, SD 0.43)	0.04 (-3.1to1.7, SD 0.87)	p=0.06

* The denominator is reduced here since those with more than one paired observation point were removed from the data and only the longest period of follow-up in each individual used for the analysis

<u>Change over time between follow-up points</u>

In 9 individuals with two paired time points. The rise in IOP between first (mean 337 days post-operatively) and second (mean 1482 days postoperatively) follow-up was 1.8mmHg in the phacotrabeculectomy eyes and 4.2mmHg in the phaco eyes (p=0.18). One individual had

acuities of 0.5 logMAR in each eye at the first follow-up and acuities of 1.5 logMAR in the phacotrabeculectomy eye and perception of light in the phaco eye at second follow-up. The remainder had a mean acuity of 0.03 logMAR units worse in the phacotrabeculectomy eyes and 0.25 logMAR units worse in the phaco eyes at second follow-up. All phaco eyes had higher IOPs at later follow-up whilst 4 (44%) of the phacotrabeculectomy eyes had further lowering of the intraocular pressure. All phaco eyes had worse acuities at later follow-up whilst 4 (44%) of the phaco-trabeculectomy eyes had further improved acuity.

DISCUSSION

This is the first study to report the effect of phacoemulsification on IOP control in African patients with POAG. We observed a much larger IOP reduction in Tanzanian patients for both procedures when compared to non-African populations reported elsewhere [10-14]. The reported IOP reduction after phacoemulsification in POAG patients does not exceed 34% in other populations [12] while we report a 41% reduction (95% CI 36-46%). Proposed reasons for IOP reduction following cataract surgery include opening of the angle. Studies have shown that the anterior chamber angle opens in all eyes after cataract extraction [18, 19, 20]. Tia M et al further noted in their study [19] that the angle widening depends on the patient's age with more angle widening in patients older than 60 years. They argue that this could be because of thicker lenses in older patients. It has been observed that after phacoemulsification the anterior chamber angle can widen and deepen by up to 50% [20]. The mean age of patients in our study was 70 years and more than 75% were at least 65 years old. Furthermore, cataract surgery results in chronic inflammation in the eye with flare in the anterior chamber persisting for up to

6 months following the procedure. Ciliary body or low grade trabecular meshwork inflammation (as in selective laser trabeculoplasty) could also result in a lowering of IOP [21]. A South African study by Cook et al in 1998 demonstrated that there is an exaggerated inflammatory response in African patients post cataract surgery which can persist up to 6 months post operatively [22]. Bhallil S et al [23] suggest that possible mechanisms of IOP reduction after phacoemulsification may include: 1) Free radicals produced during surgery may act as inflammatory mediators; ciliary body irritation by the inflammatory mediators could result in hypo secretion of aqueous humour 2) Trabecular meshwork irrigation during surgery may decrease outflow resistance 3) Increase in surgically induced production of endogenous prostaglandins may augment uveoscleral outflow and 4) phaco ultrasound stimulates production of interleukins 1α by trabecular meshwork thus increasing outflow facility and decreasing IOP.

This study addresses an important question for African populations in which most patients present very late when one eye is nearly lost from glaucoma and the other eye has advanced disease [24]. In this context, surgery is often the first line of treatment. Trabeculectomy only in African patients with co-existing cataract has an important drawback: pre-existing cataract tends to worsen, reducing vision so that within a short period of time further surgery is required to improve vision. This involves additional cost and inconvenience.

Combining the two operations in the form of phacotrabeculectomy is appealing as it addresses both the conditions. However this is not a simple procedure. It requires surgeons trained in this procedure of whom there are relatively few in Africa. Moreover, phacotrabeculectomy has

potential complications which may require further surgical interventions like bleb revision, bleb needling, or sub-Tenon's 5Fluorouracil (5FU) injections. In addition, visual gain may be compromised by an initial exaggerated inflammatory response, hypotony and refractive errors [25,26]. Frequent follow up is therefore desirable, but this may require the patient to remain close to the hospital, which may not be possible. In these circumstances, phacoemulsification surgery alone may be a better option because:

- It is technically easier
- Visual rehabilitation is faster
- There are fewer complications compared to the combined procedure
- A majority of the patients are elderly and their main concern for the remaining period of their lives is better vision for limited mobility around their surroundings. Phacoemulsification satisfies this requirement immediately postoperatively.
- Patients do not need close and frequent follow up in comparison to trabeculectomy alone or combined with phacoemulsification.

The question is whether cataract surgery alone can reduce intraocular pressure enough to slow the glaucomatous process and for how long? Our study indicates that although the IOP reduction following phacoemulsification may not be as marked as that achieved with phacotrabeculectomy, the effect did last for several years post-operatively.

A strength of this study is its within-individual design, which removes between individual variation as a source of uncertainty. However, the allocation of eyes within an individual to a particular procedure and the order of the procedures were not randomised. The eye with

the better acuity was selected for phacotrabeculectomy which was performed before phacoemulsification. Nevertheless, there were not major pre-operative differences between the eyes. The sample size of our study was small, particularly for long-term follow-up, and there may be important differences that this study was not powered to detect.

CONCLUSION

In this small study in African patients phacotrabeculectomy resulted in lower IOPs than phacoemulsification alone but the difference between the procedures was relatively small. Phacoemulsification alone was effective in reducing IOP and improving VA for several years in this population. Given the relative simplicity of phacoemulsification, it is a therapeutic option worthy of consideration in some settings.

The challenges of therapy for this blinding disease in an African context are enormous. We are currently undertaking qualitative work to investigate patient attitudes to the disease and its therapy to further inform therapeutic strategies.

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