Original Article

Comparison of effective phacoemulsification time and corneal endothelial cell loss using three different ultrasound frequencies: A randomized controlled trial

Taru Dewan, Praveen K Malik, Preeti Tomar

Purpose: Comparison of three ultrasound (US) frequencies for phacoemulsification of hard cataracts to determine a frequency that makes phacoemulsification more efficacious and safer. **Methods:** A randomized controlled trial was undertaken at a medical college and hospital. In total, 207 patients with grade 5.6–6.9 (LOCS III) senile cataract were randomized into three groups. Group I underwent phacoemulsification with 28-kHz frequency, group II with 42-kHz frequency, and group III with 53-kHz frequency. The effective phacoemulsification time (EPT) and estimated fluid usage (EFU) were compared intraoperatively. The endothelial cell parameters were analyzed for 6 months. **Results:** The groups were matched for age ($P = 0.467$), gender ($P = 0.497$), nuclear grade ($P = 0.321$), and anterior chamber depth ($P = 0.635$). The EPT and EFU were significantly lower in group III, compared to group II and group I, with $P < 0.0001$ and $P < 0.0001$, respectively. Postoperatively, the endothelial cell density (ECD) was significantly higher in group III at 1 month ($P < 0.0001$), 3 months ($P < 0.0001$), and 6 months ($P < 0.0001$). The percentages of ECD loss were also significantly lower in group III; the difference was statistically significant ($P < 0.0001$) up to 6 months postoperatively. **Conclusion:** Higher frequency ultrasound was associated with a lower EPT and EFU as well as better endothelial preservation than lower frequencies in hard cataracts.

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Frequency-based phacoemulsification is a new and logical concept. It is a much-needed panacea for hard cataracts where currently increased stroke length with its inherent effect on endothelium is the only recourse. In a previous study, use of higher frequency for phacoemulsification was associated with lower EPT and healthier endothelium up to 1-year follow-up.[1] It was proposed that the better emulsification may be due to the phacoemulsification frequency getting closer to internal resonant frequency of the cataractous lens and the endothelium sparing effect being due to more localized action of higher frequency.

A further study to identify if still higher frequency in the available range is closer to resonant frequency of hard cataracts was recommended. Thus, the present study was designed for LOCS III grade 5.6–6.9 cataracts wherein a 53-kHz sonotrode was compared with 28- and 42-kHz sonotrodes for efficacy and safety during phacoemulsification.

Methods

This randomized, parallel-group, multiple-arm trial was conducted in our institute. It was approved by the institutional ethics committee (approval number 1765/17) registered with Clinical Trials Registry of India and followed the tenets of Declaration of Helsinki.

Patients previously diagnosed with cataract reporting to the eye outpatient department of the hospital were approached to participate in the study. After a written informed consent, a detailed history was obtained. A comprehensive preoperative eye examination including specular microscopy (EM-3000, version 2A/OJ, Tomey GmbH), fundus evaluation, biometry, Snellen's visual acuity (converted to logarithm of the minimum angle of resolution), Goldmann applanation tonometry, and slit-lamp biomicroscopy was done in each patient. The cataract was graded according to the Lens Opacities Classification System III (LOCS III) classification.[2] Eyes with nuclear color (NC) of grade 5.6–6.9 were included in the study. Patients with a preoperative ECD of <1500 cells/mm^2, eye disease that could compromise visual recovery, corneal dystrophy or corneal scars preventing visualization of cataract for reliable grading, raised intraocular pressure (IOP) (>21 mm Hg), and previous intraocular surgery were excluded. All cases were recruited over 6 months starting March 16, 2018, and each case underwent surgery within 1 month from recruitment. The ECD, coefficient of variance (CV) in cell size, central corneal thickness (CCT), and hexagonal cell count (PHC) on specular microscopy and anterior chamber depth on A-scan were recorded for cases fulfilling the inclusion and exclusion criteria.

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Sample-size calculation and patient allocation

A previous study of this machine[1] found a mean EPT of 3.59 ± 2.8 s with 28 kHz, which reduced to 2.38 ± 1.93 s with 42 kHz. With a power of 80% and an alpha error of 0.05, 62 cases in each group were required to find a statistically significant difference in EPT between the groups. Taking into account an anticipated dropout of 10%, a total of 207 patients (one eye of each) who fulfilled the inclusion criteria were enrolled. Block randomization of the subjects was done by an independent observer by using a sealed envelope system. Group I had phacoemulsification with 28 kHz, group II with 42 kHz, and group III with 53 kHz (n = 69 each). The participants and outcome assessor were blinded to the intervention arm allotted.

Surgical technique

All operations were performed by one of the two surgeons (P.K.M., T.D.), each having more than 15 years of experience in phacoemulsification techniques. As per the routine protocol, the pupil was dilated with tropicamide–phenylephrine hydrochloride eye-drops every 15 min for 45 min before surgery. Plain tropicamide was used in hypertensive patients. For peribulbar block, lidocaine 2.0%, adrenaline, and bupivacaine 0.5% with hyaluronidase were used. Adrenaline was omitted in hypertensive patients. Conjunctival irrigation was done with povidone–iodine 10.0% (Betadine) solution. A 2.8-mm incision (manufacturer-recommended size) was created with a keratome. The capsulorhexis was made under sodium hyaluronate 1.4% (Zyonate). Hydroxypropyl methylcellulose 2.0% (Irimist Plus) was used for subsequent steps. Hydrodissection and rotation were completed.

All surgeries were performed using Megatron S4 HPS (Geuder) phacoemulsification machine.

Megatron works at a handpiece frequency of 27–55 kHz. The ultrasonic tip has a 30° bevel, an internal diameter of 0.6 mm, and an outer diameter of 1.0 mm without a sleeve and 1.8 mm with a sleeve. Identical parameters, except designated frequency, were used in all groups, that is, 40% US power, cool flash mode, 350-mm Hg vacuum with a dynamic rise of 1.0 s, and a bottle height of 110 cm.

Standard postoperative care was provided to all patients. Topical moxifloxacin 0.5%–prednisolone acetate 1.0% was prescribed eight times a day and then gradually tapered over 4 weeks.

Intraoperatively, EPT, EFU, and any complications were noted. Postoperative evaluation of patients was carried out by a second independent observer who was blinded to the intervention arm, and it included noncontact specular microscopy at 1 week and 1, 3, and 6 months. Endothelial cell loss was calculated as a percentage of the preoperative cell density. Intraocular pressure, Snellen visual acuity, and refraction were evaluated at 1 week and 1 month. Postoperative endothelial parameters were studied in terms of absolute values and percentage change over time. The percentages of

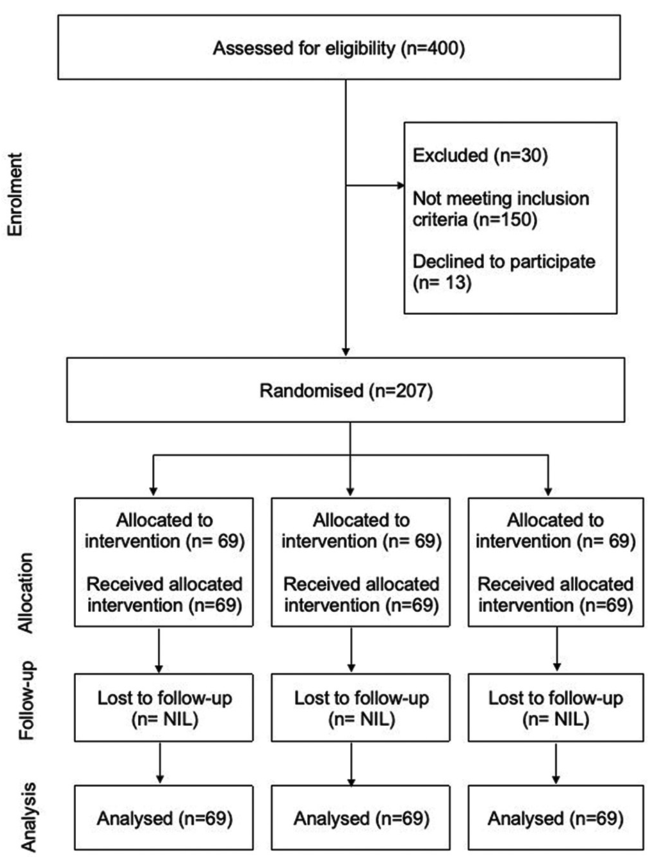

Figure 1: Participant flowchart

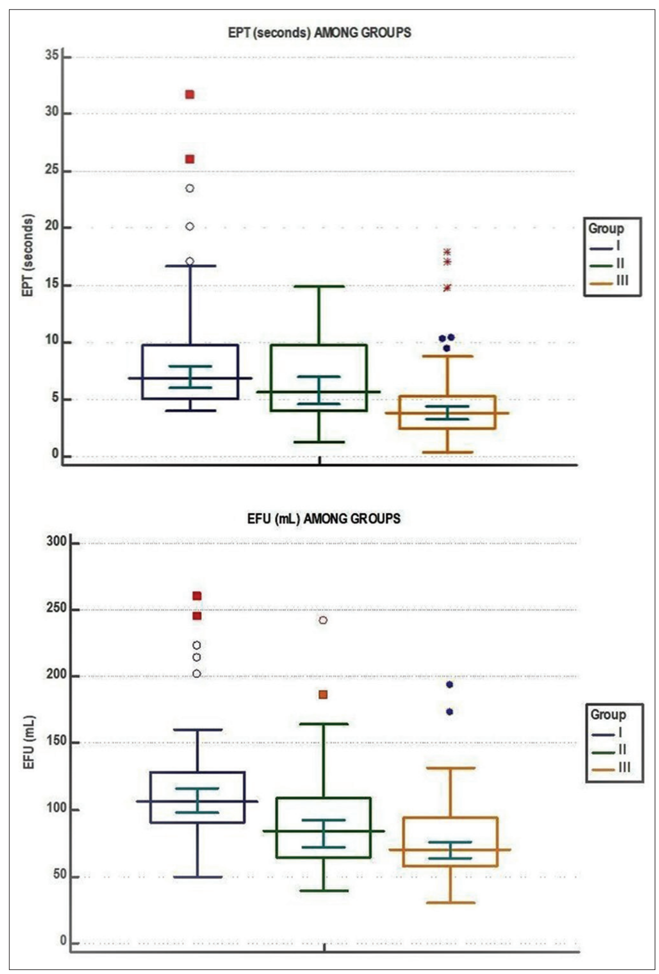

Figure 2: Comparison of effective phacoemulsification time (EPT) (in s) and estimated fluid usage (EFU) among the three groups

Table 1: Baseline parameters

		Group I (69)	Group II (69)	Group III (69)	*P*	1 vs. 2	1 vs. 3	2 vs. 3
Age (Mean + SD)		64.58±8.12	65.94±9.13	64.13±9.59	0.467	0.356	0.767	0.258
Gender	F	35 (50.72%)	35 (50.72%)	41 (59.42%)	0.497	0.865	0.392	0.392
	M	34 (49.28%)	34 (49.28%)	28 (40.58%)				
Grade (Mean + SD)		6.06±0.44	6.11±0.47	6.18±0.47	0.321	0.480	0.132	0.428
ACD (Mean + SD)		2.56±0.3	2.56±0.28	2.58±0.33	0.635	0.952	0.449	0.376

ACD: Anterior Chamber Depth, SD: Standard Deviation Age: Independent *t* test for individual *P* value and ANOVA for total *P* value; Gender: Chi-square test; Grade and ACD: Mann–Whitney test for individual *P* value and Kruskal–Wallis test for total *P* value

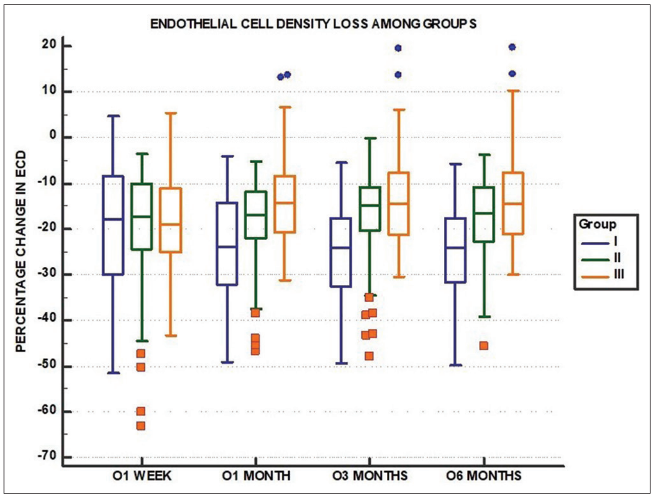

Figure 3: Comparison of change in endothelial cell density among three groups 6 six months. ECDL: percentage change in endothelial cell density

loss were calculated as the difference between the baseline value and the final values divided by the baseline value and multiplied by 100.

Statistical analysis

The data were entered in an Excel spreadsheet (Microsoft Corp.) and analyzed using Statistical Package for Social Sciences software (version 21.0, IBM Corp.) The normality of data was tested using the Kolmogorov–Smirnov test. If the normality was rejected, then a nonparametric test was used. Quantitative variables were compared using the independent *t* test and Mann–Whitney test (for nonparametric data) between the two groups and ANOVA/Kruskal–Wallis test between more than two groups. Qualitative variables were compared using Chi-square test and Fisher's exact test. The Spearman rank correlation coefficient was used to assess the relationship between quantitative parameters. $P < 0.05$ was considered statistically significant.

Results

Per the study protocol, 207 eyes of 207 patients with senile cataract were enrolled in the study and randomized into three groups. [Fig. 1]. Group I (n = 69) phacoemulsification using a 28-kHz handpiece. Group II (n = 69) phacoemulsification using a 42-kHz handpiece. Group III (n = 69) phacoemulsification using a 53-kHz handpiece. All patients completed the follow-up, and the data were subjected to analysis. All three groups were matched for age ($P = 0.467$), gender distribution ($P = 0.497$), nuclear grade ($P = 0.321$), and anterior chamber depth ($P = 0.635$) [Table 1].

Preoperative best-corrected visual acuity (BCVA) and IOP were comparable in the three groups. Mean ± SD preoperative BCVA (in logMAR scale) was 1.12 ± 0.3, 1.23 ± 0.42, and 1.22 ± 0.39 ($P = 0.176$) and IOP 15.29 ± 2.67, 15.93 ± 2.85, and 15.91 ± 2.86 ($P = 0.446$) in groups I, II and, III, respectively.

The baseline endothelial parameters were comparable in all three groups. The primary outcome variable compared was EPT, and the secondary outcome variables were ECD, CV, CCT, and PHC at 1 week, 1 month, 3 months, and 6 months, and BCVA and IOP at 1 week and 1 month postoperatively. Apart from these, EFU and incidence of PCR intraoperatively were also compared. Upon the analysis of the intraoperative readings, it was found that the EPT was significantly different among the three groups with values in the following order: group III < II < I. Similarly, EFU was also significantly different among the three groups with values in the following order: group III < II < I. [Fig. 2]

Posterior capsular rupture was noted in four cases intraoperatively, two in group I and one each in group II and group III. There was no significant difference between groups in the BCVA postoperatively at 1 week ($P = 0.646$) and 1 month ($P = 0.234$). The IOP was also comparable postoperatively at 1 week ($P = 0.441$) and 1 month ($P = 0.415$) Although all three groups had comparable baseline values of ECD, the values were significantly different among them postoperatively at 1, 3, and 6 months with values in the order: group III > II > I. [Table 2] The CV (except at 1 week), CCT, and PHC values were comparable between the groups at almost all postoperative visits. The CV was significantly lower in the higher frequency group at 1 week ($P < 0.0001$).

To get the true picture, the postoperative endothelial parameters were studied both in terms of absolute values and percentage change over time. The percentage loss in endothelial parameters was compared among any two groups by using Mann–Whitney test, while Kruskal–test was used to arrive at the total *P* value when comparing the three groups. [Table 3] The percentage loss of ECD was significantly different among the three groups with values in the order: group III < II < I over the 1, 3, and 6-month follow-up [Fig. 3] The percentage changes in CV (except at 1 week), CCT, and PHC values were comparable between the groups at almost all postoperative visits. The percentage change in CV was significantly lower in the higher frequency group at 1 week ($P < 0.0001$).

Table 2: Endothelial parameters

	Group I (69)	Group II (69)	Group III (69)	*P*
ECD Pre-op	2565.33±308.98	2495.29±283.38	2535.8±279.9	0.367
ECD 1 week	2056.54±332.44	2023.91±405.03	2064.03±212.13	0.745
ECD 1 month	1929.86±269.67	2023.7±277.62	2178.06±204.89	<.0001
ECD 3 months	1914.61±252.83	2050.07±263.53	2179.09±222.41	<.0001
ECD 6 months	1913.1±250.13	2045.04±217.85	2185±220.04	<.0001
CV Pre-op	51.04±16.88	54.81±15.43	50.04±11.7	0.170
CV 1 week	55.96±13.42	51.51±12.74	46.52±14.13	<.0001
CV 1 month	50.01±11.97	53.81±15.69	48.26±12.51	0.086
CV 3 months	47.81±12.59	51.09±12.45	48.35±10.71	0.197
CV 6 months	47.9±12.32	50.52±12.07	47.93±11.93	0.236
CCT Pre-op	499.94±36.53	508.22±34.09	504.03±33.61	0.378
CCT 1 week	537.52±51.07	536.1±39.53	529.32±36.82	0.488
CCT 1 month	521.83±34.86	520.13±44.2	513.46±38.23	0.419
CCT 3 months	516.1±34.41	511.84±41.31	505.84±34.73	0.263
CCT 6 months	508.52±32.7	505.84±38.99	502.83±36.36	0.651
PHC Pre-op	50.14±8.63	49.9±14.28	50.36±10.94	0.972
PHC 1 week	39.23±9.36	38.44±12.94	38.16±11.42	0.847
PHC 1 month	41.99±11.78	40.04±12.4	41.25±11.27	0.623
PHC 3 months	43.51±7.91	41.14±10.18	42.1±7.87	0.280
PHC 6 months	44.93±7.92	43.52±10.47	46.26±9.56	0.232

CCT: Central Corneal Thickness, CV: Coefficient of Variation of cell size, ECD: Endothelial Cell Density, PHC: Percentage of Hexagonal Cells. CCT, ECD, PHC used Independent *t* test for individual *P* value and ANOVA for total *P* value CV: Mann–Whitney test for individual *P* value and Kruskal–Wallis test for total *P* value

Table 3: Percentage change in endothelial cell density among groups

Percentage change in ECD	Group I (69)	Group II (69)	Group III (69)	*P*
ECDL 1 week				0.940
Mean±SD	−19.34±12.93	−19.13±12.85	−17.98±9.39	
Median	−17.82	−17.25	−19.04	
Min–Max	−51.6 to -4.64	−63.31 to -3.46	−43.2 to -5.51	
Interquartile Range	−29.990 to -8.323	−24.50 to -10.110	−25.049 to -10.943	
ECDL 1 month				<0.0001
Mean±SD	−24.2±11.3	−18.65±9.45	−13.45±9.6	
Median	−23.86	−16.99	−14.22	
Min–Max	−49.18 to -4.1	−46.78 to -5.3	−31.3 to -13.76	
Interquartile Range	−32.073 to -14.237	−22.010 to -11.683	−20.652 to -8.328	
ECDL 3 months				<0.0001
Mean±SD	−24.77±10.74	−17.47±9.82	−13.45±9.84	
Median	−24.09	−14.83	−14.48	
Min-Max	−49.29 to -5.44	−47.89 to -0.1	−30.42 to -19.55	
Inter quartile Range	−32.717 to -17.644	−20.344 to -10.822	−21.148 to -7.771	
ECDL 6 months				<0.0001
Mean±SD	−24.88±10.24	−17.6±8.43	−13.22±9.71	
Median	−24.23	−16.61	−14.57	
Min-Max	−49.8 to -5.77	−45.76 to -3.76	−29.92 to -19.84	
Inter quartile Range	−31.704 to -17.681	−22.784 to -10.914	−20.886 to -7.774	

ECD: Endothelial Cell Density, ECDL: Endothelial Cell Density Loss Kruskal–Wallis test for total *P* value

As anterior chamber depth can act as an important confounder in endothelial cell density loss (ECDL), we also looked for any correlation of ACD with ECDL in any of the groups.

The mean percentage ECDL was not correlated with ACD in group I, II, or III patients at any postoperative visit, rendering its effect to be insignificant in our study.

Discussion

Lens fragmentation upon interaction with phacoemulsification needle depends upon many variables, including tissue factors, which are unique to the patient, and acoustic parameters of ultrasound application, which have been repeatedly optimized to get the best efficacy.[3-5] During phacoemulsification, a needle emulsifies the lens matter by virtue of energy delivery via movement at a particular speed (frequency) through a particular distance (stroke length) and aspirating at a suction pressure (vacuum).[6-8] It has been found that suction, stroke, area of contact, acceleration (square of frequency), interaction between frequency and suction, suction and stroke, and lastly, square of frequency and stroke have a statistically significant response on fragmentability. Higher frequencies are known to increase the fragmentation rates at low stroke levels.[7]

Apart from the role of frequency on tissue disintegration, another important effect is on cavitational energy generation. The cavitation bubbles are believed to be a source of damage to endothelium by virtue of free radical formation upon each implosion.[9] *In vivo* experiments have confirmed that an ultrasound modality producing lower cavitation can lead to lower endothelial cell losses and corneal edema.[9] Low-frequency ultrasound is known to generate high cavitational energy, while it is minimal with a 50–60-kHz handpiece, which performs a smooth cutting.[10]

With the advancement of presently available surgical devices and techniques that employ ultrasound power variations, the safety and efficacy index of the phacoemulsification procedure has increased dramatically and is already touching a plateau. The aim of recent research is to reduce phaco energy and shorten the phaco time, thus reducing the damage to the corneal endothelium.[5,11] Thus, reduction in EPT and endothelial cell density (ECD) loss in cataract cases has become a promising research field.[12-14] Progressing in the same direction, we evaluated the effect of various frequencies of ultrasound during phacoemulsification. Although our study faced the limitation of being the first study on 53-kHz ultrasound in hard cataracts and thus lacking results from other observers, the fixed protocol assures us of a similar experience in the future.

Our study compared the EPT and endothelial cell density loss using handpieces of three different ultrasound frequencies (28, 42, and 53 kHz) with the same machine for phacoemulsification of hard cataract grade 5.6–6.9 (LOCS III grading). We found that the EPT was significantly lower in group III compared to group I ($P < 0.0001$) as well as group II ($P < 0.0001$), suggesting that the higher frequency effectively lowers the EPT. Earlier two studies had proven the superiority of 42 kHz over 28 kHz and had given a direction for further search to arrive at an optimally high frequency.[1,15] There has been no published work to study the effect of three different US frequencies for phacoemulsification using the same machine in literature to date. The lower EPT in hard cataracts might be due to our reaching closer to the optimal frequency (53 kHz) required for tackling these cataracts.

Large infusion volumes can increase the risk of endothelial cell loss after phacoemulsification.[16] Thus, analysis of EFU becomes important in hard cataract cases. Similar to EPT, EFU was significantly lower in group III as compared to group I ($P < 0.0001$) and II ($P = 0.008$). This again was in line with the previous study using two frequencies.[1]

The ultimate measure of safety is often taken to be intraoperative complications and endothelial health during follow-up. All three groups had a similar incidence of posterior capsular rupture. Postoperatively, changes in ECD, CV, CCT, and PHC were studied at 1 week, 1 month, 3 months, and 6 months. There was no statistically significant difference in ECD between three groups at 1 week ($P = 0.745$), but subsequently, the difference was statistically significant at 1 month ($P < 0.0001$), 3 months ($P < 0.0001$), and 6 months ($P < 0.0001$). In addition, the percentage loss of ECD was significantly lower in group III in comparison to groups I and II, and the difference was statistically significant at all postoperative visits, except 1 week ($P = 0.940$). The lesser endothelial cell loss in group III (53 kHz) indicates the salvaging effect of higher frequency over corneal endothelium. An important factor contributing to the effect on corneal endothelial health could be the low cavitational energy produced during phacoemulsification with 53 kHz as compared to 28- and 42-kHz handpieces. This cavitational energy, an essential factor in tissue disintegration, also leads to the generation of free radicals responsible for endothelial cell destruction.[17] An *in vivo* experiment showed free radical genesis during phacoemulsification causing ECL and corneal edema.[9] Another study[18] showed that free radical concentration was proportional to US duration. Thus, we expect a procedure with lower phaco time and lower cavitation to generate fewer free radicals.

Our present study establishes that an increase in ultrasound frequency not only reduces EPT and EFU but also preserves endothelium. The benefits of increasing frequency had not been realized even though the principle was incorporated when going from continuous mode to pulse and micropulse modes. Similarly, when a 45% increase in frequency was done in Ellipse FX (38 kHz) from the previous version, the focus remained on stroke length for the improvement.[19] While debates on benefits of torsional phacoemulsification over longitudinal primarily stood ground on the proposed better cavitational effect, it was also suggested that if cavitation is representative in emulsification power as a single cut at the nucleus, the four cuts per vibration of torsional phaco works the same as a phacotip operating at 125 kHz.[20] An ultra-high-speed video was used to arrive at the same as shown earlier on hard nuclei.[21] Even if the cavitation effect is contributory, incorporating high frequency in torsional phacoemulsification may add the benefit of resonant frequency-induced changes in lens matter and subsequent tissue disintegration.

The studies have clearly established that an increase in stroke length increases fragmentability, but endothelial losses and complications also increase.[16,19,22,23] However, frequency modulation has been a largely unexplored realm. We find it very promising and logical. It may simplify our understanding of the very mechanism behind lens tissue disintegration. In addition, we are getting increased safety with an increase in frequency as seen in previous studies and confirmed by the present one.[1,9] The very concept of resonant frequency of target tissue has been promoted in previous works and studies.[1,15] The resonant frequency of a solid matter can be assessed by subjecting samples to a range of frequencies and analyzing the effects as in the present study, which is an *in vivo* attempt to arrive at the ideal frequency for hard cataracts. The other approach is by studying either the physical properties to identify sonic resonance using viscoelasticity models or optical properties with relevant apparatus such as Raman spectroscopy.[24,25]

We strongly recommend the concept of variable frequency phacoemulsification for different grades of cataracts and hope for the development of a tunable frequency phacoemulsification machine within our lifetime. We continue our endeavors to strengthen and refine the concept till we arrive at a perfect algorithm between the grade of cataract and optimal frequency for different phacoemulsification machine designs.

Conclusion

In this study we found that use of higher frequency sonotrode (53KHz) for phacoemulsification was associated with lower EPT and healthier endothelium as compared with 42 KHz and 28KHz sonotrodes. We feel that this higher frequency in available range is closer to resonant frequency of the hard cataract. If we are able to quantify the resonant frequencies of the biomolecules in every grade of cataract, the lens can be liquified non thermally by delivering frequency matched ultrasonic or light energy.

This reinforces the need to conceptualise and design a tunable frequency phacoemulsification machine based on a perfect algorithm between grade of cataract and its optimal frequency.

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Conflicts of interest

Patent pending: Authors 1 and 2 are coinventors in International Application under No.: PCT/DE2018/200069 dated: 23.07.2018 for the invention titled, "Ophthalmological handheld device and sonotrode for an ophthalmological handheld device."

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