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Factors influencing pupil behaviour during femtosecond laser assisted cataract surgery

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ABSTRACT

Aim: Femtosecond laser assisted cataract surgery is associated with pupillary constriction. This study aims to look at patient and surgical factors predisposing to abnormal pupil behaviour during FLACS.

Methods: This prospective observational study included all patients undergoing FLACS in the Princess of Wales Hospital, Bridgend, UK between February and June 2017. Pupils were measured at three time points; immediately before and after laser pre-treatment, and at the start of surgery. Pupil behaviour during surgery was noted in descriptive terms, patient demographic, co-morbidities, eye measurements, suction on time, shifting time and laser energy levels were recorded.

Results: Seventy-three eyes were included. Average patient age was 74.84 ± 9.1 years. Mean horizontal pupil sizes immediately before and after femto pre-treatment were 7.87 ± 0.87 mm and 7.7 ± 0.89 mm respectively ($P < 0.0005$). Mean horizontal pupil size at the start of surgery was 6.83 ± 1.43 mm ($P < 0.0005$). Short capsulotomy–pupil distance ($P = 0.01$), shallower anterior chamber ($P = 0.0012$), smaller pre-operative pupil size ($P = 0.045$) and longer suction on time ($P = 0.0019$) were significantly associated with intra-operative miosis during FLACS. Sustained mydriasis was observed in eyes in whom topical diclofenac was used within 2 h of surgery.

Conclusions: FLACS can result in significant pupil miosis. Eyes particularly at risk are ones with smaller pre-operative pupils and shallower anterior chambers and those subjected to longer suction on time. Well-timed NSAIDs application could be protective against this phenomenon.

1. Introduction

Femtosecond laser has been used for cataract surgery since 2008 [1]. It operates at the near infrared light range (wavelength 1053 nm) delivering ultra short (10^{-15}) light pulses. The laser energy generates cavitation by the formation of gas bubbles that expand and coalesce leading to cleavage of tissues [2,3]. Pupil constriction, induced by the femtosecond (femto) laser, is the most frequent problem encountered by this new technology with prevalence of up to 32% [4]. Small pupil size has been linked to increased risk of complications during conventional cataract surgery, namely iris trauma, uveitis, anterior capsule tears, zonular dehiscence, posterior capsule rupture and vitreous loss [5]. It is speculated that femto-induced miosis is driven by inflammatory mediators released in response to laser energy, although the exact mechanism is currently unknown. Increased levels of prostaglandins (PGs) and other inflammatory mediators have been demonstrated in the aqueous humor after femtosecond laser treatment, with capsulotomy inducing highest inflammatory response [6–8]. A recent study by Jun et al. confirmed that the topical non-steroidal anti-inflammatory drugs (NSAIDs) can significantly reduce the risk of intraoperative miosis, but other patient and surgical factors play part [4,9]. Many factors, which affect pupil size, have not been extensively studied in femtosecond laser assisted cataract surgery (FLACS) [10]. The current study aimed to find patient and surgical factors influencing pupil behaviour during FLACS to identify how best to mitigate femto-induced miosis.

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2. Patients and methods

This prospective observational study was approved by the Abertawe Bro Morgannwg University Health Board Research and Development department in conjunction with the University of Ulster. All patients, who underwent femtosecond laser assisted cataract surgery (FLACS) with the VICTUS femtosecond laser platform (Bausch and Lomb, Rochester, New York, USA) in the Princess of Wales Hospital, Bridgend, United Kingdom between February and June 2017 were included. Two experienced surgeons (VK and MP) performed all surgeries under topical anaesthetic. Preoperatively patients received a combination of two dilating drops; cyclopentolate 1% and phenylephrine 2.5%, applied three times each before surgery, and topical diclofenac (Voltarol Ophtha 0.1%, Thea Pharmaceuticals, Newcastle Under Lyme, UK). All patients underwent capsulotomy and lens fragmentation by the VICTUS platform followed by immediate transfer for the remainder of their surgery. Capsulotomy size varied between 5.0 and 5.2 mm, with pulse energy set at 6.76 μJ, 6.5 μm spot and 6 μm line spacing. Lens fragmentation pattern into four quadrants was used with pulse energy of 8.11 μJ, 7.8 μm spot and 12 μm line spacing. In order to quantify pupil size during FLACS three horizontal pupil measurements were taken by one investigator (MP) using the external surgical ruler. External pupil measurements were performed immediately before and after femto pre-treatment and at the start of surgery, before corneal incisions were made. Beyond that pupil behaviour was noted in descriptive terms, as observed by two investigators (VK and MP). The use of additional mydriatic aids and intraoperative complications were recorded. All procedures were performed with adrenaline infused irrigating solutions. First external pupil measurement was correlated with pupil size measured by the laser. The laser estimates pupil size as a best-fit circle via patient interface using safety margin of 500 μm between the fragmentation size and pupil edge. Laser pupil size was used for calculation of the distance between capsulotomy and pupil edge. Demographic patient data, eye dimensions from biometry printouts, time of pre-operative drops application, total energy used, suction on time and time between femto pre-treatment and start of manual incisions (defined as shifting time) were recorded.

2.1. Statistics

The *T*-test was used to compare the reduction in the pupil size measurements between different time points, and to detect significant differences between continuous variables and anomalous pupil behaviours during FLACS. A Chi-square test was used to analyse statistically significant associations between pupil behaviour and nominal variables. Pearson correlation analyses were used to identify correlations between pupil size measurements by ruler and by the laser, as well correlations of variables to changes in pupil size. Multivariate analysis was performed for data suited to this analysis. The multivariate tests did not add to the conclusions. Statistical significance was defined with a *P* value of equal to or less than 0.05. All statistical analyses were performed using SPSS software (version 20.0, IBM Corp, Armonk, NY, USA).

3. Results

Seventy-three eyes of sixty-seven patients were included. Forty-three patients were women (59%) and twenty-four men (41%) with an overall mean age of 74.84 ± 9.1 years (36–90 years). All operated patients were Caucasian, 73% had blue, 21% – brown and 6% green – brown eye colour. Mean axial length was 23.80 ± 1.45 mm (21.40–28.63 mm). Mean pre-operative spherical equivalent was −0.52 ± 2.99 Diopters (D) (−9.3 to +5.7 D) and the mean corneal astigmatism was 1.05 ± 0.58 D.

Mean number of systemic co-morbidities was 2.4 with treated high blood pressure affecting 64% of patients and Type 2 Diabetes mellitus in 16% of patients. Known risk factors for intraoperative floppy iris syndrome (IFIS) and small pupils were as follows: 3 patients were on doxazosin, 2 on tamsulosin and 3 eyes had pseudoexfoliation syndrome (PXF). Fifteen patients were taking oral aspirin or NSAIDs and 10 were on systemic steroids (inhaled or oral preparations). Doses were not recorded.

Mean horizontal pupil sizes immediately before and after femto pre-treatment were 7.86 ± 0.86 mm and 7.7 ± 0.89 mm respectively ($P < 0.005$). Mean laser pupil pre-treatment measurement was 6.76 ± 0.63. A strong positive correlation between manual external horizontal pupil and laser pupil measurements was found (Pearson's $r = 0.68$, $P = 0.0005$).

Mean suction on and mean shifting times were 2.71 ± 1.49 min and 4.22 ± 1.6 min respectively. Mean horizontal pupil size at the start of surgery was 6.84 ± 1.44 mm, with mean horizontal pupillary miosis of 1.02 ± 1.09 mm between the start of femto pre-treatment and surgery ($P < 0.005$).

Significant miosis, defined as pupil size equal to or less than capsulotomy size at the start of surgery, was noted in 17 eyes (23%). Progressive miosis and/or floppy iris during surgery was observed in further 23 eyes (32%). Sustained mydriasis with no noticeable miosis or iris floppiness was observed in 33 eyes (45%). Significantly shorter mean capsulotomy–pupil distances and smaller pre-operative pupil sizes were noted in the eyes affected by significant miosis compared to eyes with sustained mydriasis (Table 1).

Analysis was carried out to identify associations with anomalous pupil behaviour. Shorter distance between pupil edge and capsulotomy was significantly associated with a reduction in pupil size ($P = 0.01$). A strong negative correlation between the size of the pupil pre-treatment and the amount of intraoperative miosis was noted (Pearson's $r = -0.800$, $P < 0.005$). Anterior chamber depth shallower than 3 mm was associated with progressive intraoperative miosis and/or floppy iris ($P = 0.012$). Suction on time longer than 2 min was also associated with significant miosis ($P = 0.0019$).

Parameters not significantly associated with abnormal pupil behaviour during surgery were age ($P = 0.44$), axial length ($P = 0.673$), spherical equivalent ($P = 0.343$), eye colour ($P = 0.456$), presence of treated hypertension ($P = 0.308$), Diabetes mellitus ($P = 0.466$),

Table 1
Comparison between eyes, where pupil less than capsulotomy size was noted at start of surgery with eyes, where sustained mydriasis was observed. [CCC- capsulotomy, ACD- anterior chamber depth].

Parameter	Pupils less than capsulotomy size at start of surgery (n = 17)	Sustained mydriasis during surgery (n = 33)	P value
Mean age	75.11 ± 10.65 years	77.45 ± 5.84 years	0.157
Mean axial length	23.27 ± 1.01 mm	23.69 ± 1.09 mm	0.096
Mean CCC- pupil distance	**0.77 ± 0.17 mm**	**0.99 ± 0.29 mm**	**0.003**
Mean ACD	3.12 ± 0.42 mm	3.21 ± 0.46 mm	0.258
Mean pre-operative laser pupil size	**6.675 ± 035 mm**	**7.12 ± 0.60 mm**	**0.004**
Mean suction on time	2.95 ± 1.70 min	2.73 ± 1.45 min	0.236
Mean laser energy	14.43 ± 1.98 μJ	14.76 ± 1.55 μJ	0.275
Mean time of NSAIDs to surgery	**153.17 ± 63.38**	**118.90 ± 61.88 min**	**0.04**

patient weight ($P = 0.819$), total laser energy ($P = 0.78$) and shifting time ($P = 0.07$). The use of alpha antagonists ($P = 0.380$), oral NSAIDs or aspirin ($P = 0.398$), and systemic use of steroids ($P = 0.352$) also did not reach statistical significance but overall patient numbers in each category were low.

Intracameral phenylephrine was used in 24 eyes (33%). No mechanical expanders were necessary in this series. There were significant differences in mean times of topical NSAIDs application before FLACS between eyes affected by intraoperative miosis and eyes that had sustained mydriasis ($P = 0.04$). Eyes, which received NSAIDs within 2 h prior to start of FLACS, were more likely to show sustained mydriasis during surgery (Table 1).

Anterior capsule tear was noted in two eyes, both had intraoperative miosis ($P = 0.417$). Post-operatively two eyes required treatment for post-operative uveitis (2.7%) and two eyes developed cystoid macular oedema (2.7%), none had pupil problems at the time of surgery.

4. Discussion

Femtosecond laser treatment is associated with pupillary constriction, potentially lessening surgical benefit of this technology [11,12]. In our series the intraoperative complications were not significantly associated with incidence of intraoperative pupil miosis. The exact mechanism of femto-induced miosis is unknown, but seems to be driven by inflammatory mediators [6]. Increased levels of prostaglandins (PGs) and interleukins IL-1β, IL-6 have been noted in femto treated patients. These increases were found to be independent of patient age, cataract density, suction on time, laser time, and creation of corneal incisions by the laser [6,7]. A recent study by Jun et al. found no correlation between the levels of prostaglandins and the amount of pupil constriction during FLACS, suggesting that any increase in PGs can lead to this phenomenon [9]. The use of topical non-steroidal anti-inflammatory drugs (NSAIDs) preoperatively has been shown to help reduce the risk of intraoperative miosis during FLACS, however optimal timing of their application is unknown. Also sole use of NSAIDs does not negate the phenomenon of femto-induces miosis completely, suggesting other factors play part [4,9,13–15].

There is a wide variation of femto-induced miosis prevalence (1.26–32%) reported in the literature, related to lack of standardised agreement of what is considered 'surgically significant', as well as different pre-operative dilating and NSAIDs drop regimes [4,13,16–18]. In our series we defined significant miosis as pupil constriction to the size of capsulotomy or less. Seventeen eyes (23%) were affected by significant miosis at the start of surgery and further seven eyes experienced surgically significant miosis necessitating use of intracameral phenylephrine during surgery. Short capsulotomy–pupil distance as well as shallower anterior chamber were associated with anomalous pupil behaviour. The amount of pupil constriction was negatively correlated to the size of pre-operative pupil, suggesting that smaller pupils are particularly at risk of femto-induced miosis. Our findings support the theory that it is the gas bubbles created during capsulotomy, which irritate pupil edge and lead to prostaglandins release with subsequent pupillary constriction [8]. Our findings agree with previously published work by Jun et al., who also described significant correlation of pupillary miosis with shorter capsulotomy–pupillary distance [11]. A study by Pahlitzsch et al. found higher levels of flare immediately after FLACS in eyes with shallow anterior chambers [19]. Thus implicating smaller anterior chamber space during FLACS as a predisposing factor for the inflammatory response. Since inflammation is the driving force for pupillary constriction in FLACS, this corresponds with our finding of shallower anterior chambers being associated with subsequent miosis. Longer suction on time was associated with pupillary miosis in our series. Previous studies failed to correlate suction on time with pupillary miosis [6,11], but there have been suggestions that a raise in intraocular pressure during suction might also be an initiating factor for PGs release and could be partially responsible for pupillary miosis [3,20].

It is already known that the pre-operative use of NSAIDs is incapable of preventing femto-induced miosis in all cases, the optimal timing of NSAIDs application is unknown [9]. Based on our results it is reasonable to suggest, that if pre-operative diclofenac is being used on the day of surgery, sustained mydriasis can be anticipated when FLACS is performed within the first 2 hours of drop application. This agrees with the manufacturer's recommendation based on drug pharmacokinetics [21]. A single topical application of 0.1% diclofenac reaches peak aqueous concentrations at 2.4 hours, but the drug is present in the aqueous humor within minutes of application with levels rising in a linear fashion [22–24].

Oral aspirin has been shown to help in achieving sustained mydriasis in eyes undergoing extracapsular cataract extraction [25]. The use of systemic NSAIDs, aspirin and systemic steroids was not found to be protective against pupillary constriction in our series, likely relating to low ocular levels, low patient numbers and different method of cataract extraction. The use of alpha agonists was not associated with pupil constriction but overall numbers were low and subject to numerical bias. This was an observational study and was not powered to detect differences between all studied variables.

In our study external pupil measurements were taken with a ruler to estimate the amount of pupil constriction. To validate our method, pupil measurements by ruler were correlated with the laser measurements, and a strong positive correlation was found. Nevertheless both ruler and laser pupil measurements are subject to error due to corneal magnifications [26].

Pupil behaviour during surgery was noted in descriptive terms. Pupil behaviour during standard surgery can be affected by various factors including light intensity, phacoemulsification time, energy, and iris touch [27]. The effect of these on pupil behaviour could not be fully excluded.

In summary femto-induced miosis is likely a multifactorial phenomenon. Our results suggest that the laser induces miosis due to iris irritation during treatment. Eyes, which have been subject to longer suction on times, as well as those with smaller preoperative pupils and shallower anterior chambers, predisposing to short capsulotomy–pupillary distance, are most susceptible. Well-timed addition of topical NSAIDs to the dilating regime is protective against this phenomenon.

Conflict of interest

The authors declare no conflict of interest. Study was undertaken as part of Masters Degree in Cataract and Refractive Surgery via the University of Ulster, UK by the first author.

References

[1] Z. Nagy, A. Takacs, T. Filkorn, M. Sarayba, Initial clinical evaluation of an intraocular femtosecond laser in cataract surgery, J Refract Surg 25 (2009) 1053–1060.
[2] A. Agarwal, S. Jacob, Current and effective advantages of femtophacoemulsification, Curr Opin Ophthalmol 28 (1) (2017) 49–57.
[3] K.E. Donaldson, R. Braga-Mele, F. Cabot, R. Davidson, D.K. Dhaliwal, R. Hamilton, et al., Femtosecond laser-assisted cataract surgery, J Cataract Refract Surg 39 (2013) 1753–1763.
[4] Z.Z. Nagy, A.I. Takacs, T. Filkorn, K. Kránitz, A. Gyenes, É. Juhász, et al., Complications of femtosecond laser-assisted cataract surgery, J Cataract Refract Surg 40 (1) (2014) 20–28.
[5] N. Narendran, P. Jaycock, R.L. Johnston, H. Taylor, M. Adams, D.M. Tole, et al., The Cataract National Dataset electronic multicentre audit of 55 567 operations: risk stratification for posterior capsule rupture and vitreous loss, Eye 23 (2009) 31–37.
[6] T. Schultz, S.C. Joachim, M. Kuehn, H.B. Dick, Changes in prostaglandin levels in patients undergoing femtosecond laser-assisted cataract surgery, J Refract Surg 29 (11) (2013) 742–747.
[7] L. Wang, Z. Zhang, D.D. Koch, Y. Jia, W. Cao, S. Zhang, Anterior chamber interleukin 1β, interleukin 6 and prostaglandin E2 in patients undergoing femtosecond laser-assisted cataract surgery, Br J Ophthalmol 100 (4) (2016) 579–582.
[8] T. Schultz, S.C. Joachim, M. Stellbogen, H.B. Dick, Prostaglandin release during femtosecond laser-assisted cataract surgery: main inducer, J Refract Surg 31 (2) (2015) 78–81.

[9] J.H. Jun, Y.S. Yoo, S.A. Lim, C.K. Joo, Effects of topical ketorolac tromethamine 0.45% on intraoperative miosis and prostaglandin E2 release during femtosecond laser-assisted cataract surgery, J Cataract Refract Surg 43 (4) (2017) 492–497.
[10] H. Hashemi, M.A. Seyedian, M. Mohammadpour, Small pupil and cataract surgery, Curr Opin Ophthalmol 26 (1) (2015) 3–9.
[11] J.H. Jun, K.Y. Hwang, S.D. Chang, C.K. Joo, Pupil-size alterations induced by photodisruption during femtosecond laser-assisted cataract surgery, J Cataract Refract Surg 41 (2) (2015) 278–285.
[12] H.B. Dick, R.D. Gerste, T. Schultz, Laser cataract surgery: curse of the small pupil, J Refract Surg 29 (10) (2013) 662.
[13] R. Yeoh, Intraoperative miosis in femtosecond laser-assisted cataract surgery, J Cataract Refract Surg 40 (5) (2014) 852–853.
[14] T. Schultz, S.C. Joachim, M. Szuler, M. Stellbogen, H.B. Dick, NSAID pretreatment inhibits prostaglandin release in femtosecond laser-assisted cataract surgery, J Refract Surg 31 (12) (2015) 791–794.
[15] H.J. Kiss, A.I. Takacs, K. Kranitz, G.L. Sandor, G. Toth, B. Gilanyi, et al., One-day use of preoperative topical nonsteroidal anti-inflammatory drug prevents intraoperative prostaglandin level elevation during femtosecond laser-assisted cataract surgery, Curr Eye Res 41 (8) (2016) 1064–1067.
[16] T.V. Roberts, M. Lawless, S.J. Bali, C. Hodge, G. Sutton, Surgical outcomes and safety of femtosecond laser cataract surgery: a prospective study of 1500 consecutive cases, Ophthalmology 120 (2013) 227–233.
[17] S.J. Bali, C. Hodge, M. Lawless, T.V. Roberts, G. Sutton, Early experience with the femtosecond laser for cataract surgery, Ophthalmology 119 (5) (2012) 891–899.
[18] R.G. Abell, E. Darian-Smith, J.B. Kan, P.L. Allen, S.Y.P. Ewe, B.J. Vote, Femtosecond laser-assisted cataract surgery versus standard phacoemulsification cataract surgery: outcomes and safety in more than 4000 cases at a single center, J Cataract Refract Surg 41 (2015) 47–52.
[19] M. Pahlitzsch, N. Torun, M.L. Pahlitzsch, M.K.J. Klamann, J. Gonnermann, E. Bertelmann, et al., Correlation between anterior chamber characteristics and laser flare photometry immediately after femtosecond laser treatment before phacoemulsification, Eye 30 (2016) 1110–1117.
[20] V.F. Diakonis, N. Yesilirmak, I.O. Sayed-Ahmed, D.P. Warren, G.A. Kounis, Z. Davis, et al., Effects of femtosecond laser-assisted cataract pretreatment on pupil diameter: a comparison between three laser platforms, J Refract Surg 32 (2) (2016) 84–88.
[21] Voltarol Ophtha Multidose – product specification detail. Available at https://www.medicines.org.uk/emc/medicine/27016. Accessed on 13.07.2017.
[22] M. Palmero, J.L. Bellot, N. Alcoriza, C. García-Cabanes, A. Orts, The ocular pharmacokinetics of topical diclofenac is affected by ocular inflammation, Ophthalmic Res 31 (1999) 309–316.
[23] S.J. Kim, A.J. Flach, L.M. Jampol, Non-steroidal anti-inflammatory drugs in ophthalmology, Surv Ophthalmol 55 (2) (2010) 108–133.
[24] P.P. Ellis, D.S. Pfoff, D.C. Bloedow, H. Riegel, Intraocular diclofenac and flurbiprofen concentrations in human aqueous humor following topical application, J Ocul Pharmacol Ther 10 (1994) 677–682.
[25] K.N. Rao, M.V. Rao, Role of aspirin in cataract surgery, Indian J Ophthalmol 33 (2) (1985) 89–90.
[26] F.F. Marques, D.M.V. Marques, R.H. Osher, New technique to demonstrate corneal magnification using trypan blue in cataract surgery, Rev Bras Oftalmol (4) (2011) 235–237.
[27] A. Zaczek, C. Zetterström, Cataract surgery and pupil size in patients with diabetes mellitus, Acta Ophthalmol Scand 75 (4) (1997) 429–432.