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Effect of Intracameral Injection of Preservative Free, Fixed Concentration of Combined Mydriatic plus Anaesthetic Formulation on Corneal Endothelial Cell Count in Phacoemulsification

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Research Article

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Abstract

Purpose: To evaluate the efficacy and safety of intracameral injection of a standardized combination of tropicamide 0.02%, phenylephrine 0.31% and lidocaine 1% on corneal endothelial cell count at phacoemulsification.

Methods: In this prospective randomized controlled study, 30 eyes of 30 patients undergoing phacoemulsification were assigned to 2 groups. 15 eyes (Intracameral Group A) received 0.2ml of a combination of tropicamide 0.02%, phenylephrine 0.31% and lidocaine 1% just after the first incision. While 15 eyes (Group B) received a topical regimen of one drop of each of cyclopentolate hydrochloride 1% and tropicamide 1%, every 15min for 1hour preoperatively. The main outcome measures were safety on corneal endothelium, by comparing the preoperative and 3 weeks postoperative corneal endothelium cell count in the two groups. Efficacy was also evaluated by measuring pupil size before capsulorhexis and before intraocular lens implantation, in both groups.

Results: There was no significant statistical difference in the percentage of endothelial cell loss between the Groups A (27.4%) and the reference Group B (25.7%), with P value (0.595). Regarding Pupillary dilatation, adequate dilatation (>7.4mm) was achieved in both groups. Dilatation was maintained to the end of operation in the Fydrane group, while in the reference group, reduction in pupillary dilatation occurred in 20% (3 cases) reaching pupil diameter 5.5mm before IOL implantation.

Conclusions: This study showed that intracameral injection of tropicamide 0.02%, phenylephrine 0.31% and lidocaine 1% is safe on corneal endothelium and effective in maintaining pupillary dilatation throughout the surgery.

Keywords: Fydrane; Mydriasis; Intracameral Mydriatic; Mixed Mydriatic; Anaesthetic Combination; Endothelial Cell Count

Abbreviations: IOL: Intraocular Lens Implantation; NSAIDs: Non-Steroidal Anti-inflammatory Drugs; IC: Intracameral; AC: Anterior Chamber; MSICS: Manual Small Incision Cataract surgery.

Introduction

Cataract surgery is the most commonly performed surgical procedure worldwide. There is good evidence to show that cataract extraction with intraocular lens implantation is one of the most beneficial procedures to improve a patient's quality of life [1]. Adequate mydriasis is crucial for performing uneventful cataract surgery. Inadequate pupil dilation is associated with increased risk for intraoperative complications, including iris injury, incomplete removal of cortical and nuclear materials, and posterior capsule rupture [2].

Traditionally, surgeons use a combination of topical sympathomimetics (phenylephrine) and parasympatholytics (tropicamide, cyclopentolate) to achieve mydriasis before cataract surgery. In the context of ocular pharmacology, the bioavailability of topical medications has always been suboptimal. Only about 20% of a drop is retained in the cul-de-sac. The rapid turnover of the fluid in the tear reservoir of 16% per minute also reduces the amount of the drug [3]. This poor bioavailability not only leads to delay in the onset of mydriasis, but also causes cardiovascular side effects through systemic absorption via nasal mucosa [4].

Using intracameral mydriatics for cataract surgery avoids the issues of poor bioavailability, prolonged duration of action, and corneal epithelial toxicity associated with eyedrops. It also provides almost instant action. Intracameral dilation was first reported in 2003, with the use of non-preserved lidocaine hydrochloride 1.0% [5]. In the last few years, manufacturers all over the world have worked together, and currently there are 2 approved premade products for intracameral mydriasis: Omidria and Fydrane. Omidria is a commercially available FDA-approved combination drug product containing phenylephrine 1.0% and ketorolac 0.3%, a nonselective cyclooxygenase inhibitor approved for use during cataract surgery. This standardized premade combination represents a new treatment option for surgeons to address intraoperative miosis and postoperative ocular pain. Although patients still require topical dilating drops, this combination drug, used in the irrigating solution, has been shown to be effective in maintaining mydriasis [6].

Fydrane is the first commercially available intracameral mydriatic and anaesthetic mixture licensed for use during cataract surgery. It is comprised of a standardized combination of tropicamide 0.02%, phenylephrine 0.31%, and lidocaine 1.0%. First launched in Italy in 2016, this product is currently licensed for use in all 27 countries in the European Union [7]. The inclusion of lidocaine in Fydrane augments the effect of topical anaesthetic, producing better intraoperative anaesthesia. The anaesthetic agent in Fydrane is a response to a medical need suggested by the off-label use of IC anaesthetics to improve patient comfort intraoperatively. Traditional preoperative topical anaesthesia may be insufficient during surgery, especially during IOL insertion [8]. Previous studies have shown that 1% IC lidocaine does not cause endothelial cell toxicity. It induces serum concentrations of lidocaine that are below minimum detectable levels and it does not diffuse into the posterior segment (even with 500µL injection). An additional benefit is the mild mydriatic effect of IC lidocaine [9,10].

Patients & Methods

Patient's Data and Study Design

This prospective randomized control study was approved by the local ethical committee of Kasr Alainy Hospital-Cairo University and was in accordance with the tenets set forth in the Declaration of Helsinki. All participating patients were informed about the procedure and possible risks, and signed informed consents were obtained.

This study was conducted between March 2019 and August 2019. The study enrolled patients aged between 60 and 75 years old having medium density cataract (nuclear II to III) scheduled to undergo phacoemulsification with foldable IOL implantation under local anaesthesia with clear self-sealing corneal incisions. Only one eye per patient could be included in this study. Exclusion criteria included ages below 60 and above 75, soft or hard cataracts (nuclear density I or IV), Iatrogenic, congenital or traumatic cataract, associated eye disease e.g. pseudoexfoliation syndrome, associated pre-existing corneal endothelial disease e.g. Fuchs dystrophy, or associated systemic disease that can affect endothelium,. Also, any history of ocular trauma or previous intraocular surgery was excluded. At the initial selection visit, a pupil diameter of at least 7 mm had to be obtained within 60 min following instillation of one drop of tropicamide 1% and one drop of cyclopentolate hydrochloride 1% (maximum of four combined instillations at 15 min intervals, if necessary), otherwise, the patient was excluded. The study included 30 eyes of 30 patients, divided into two groups (15 patients in each group). Patients were assigned randomly in each group.

Group A (15 patients) (Fydrane group) did not receive any topical dilating eye drops preoperatively. They were injected with intracameral Fydrane to dilate the pupil intraoperatively. Fydrane was administered at the beginning of cataract surgery after the first incision, at a dose of 0.2ml of solution, in only one injection. Fydrane®: (Manufacturer DELPHARM TOURS, FRANCE).

The active substances in Fydrane are: tropicamide 0.04mg (anticholinergic), phenylephrine hydrochloride 0.62mg

(alpha sympathomimetic) and Lidocaine hydrochloride 2mg (amide type local anaesthetics) for each 0.2ml dose, equivalent to 0.2mg of tropicamide, 3.1mg of phenylephrine hydrochloride and 10mg of lidocaine hydrochloride for 1ml.

Group B (15 patients) (Reference group) was not injected with intracameral Fydrane. Pupillary dilatation in this group was achieved using preoperative topical eye drops: cyclopentolate hydrochloride 1% and tropicamide 1% one drop every 15min for 1hour preoperatively.

Procedure

Both groups received peribulbar anaesthesia preoperatively. Surgeries in both groups were done by the same surgeon (M.H.) using same phaco parameters, by the same phaco machine (Infiniti, Alcon). Pupillary dilatation was assessed by measuring pupil diameter using surgical caliper at specific steps of surgery: before capsulorhexis and before IOL implantation.

All patients had a complete ophthalmic history and examination which included refraction assessment of uncorrected and best-corrected visual acuity, slit-lamp bio-microscopy of the anterior and posterior segments, Goldman applanation tonometry and dilated fundus examination. All patients received same postoperative medications. Patients were followed up first day postoperative, after 1 week and after 3weeks. Specular microscopy was done preoperatively and 3 weeks postoperatively to all patients on same machine (SP 3000P, Topcon).

Primary outcome evaluates safety of Fydrane assessed by comparing pre and postoperative endothelial cell count and calculating percentage of endothelial cell loss in both groups. Secondary outcome is Fydrane Efficacy; which is evaluated by measuring pupil diameter using surgical caliper at certain timings during surgery (before capsulorhexis and before IOL implantation) in both groups.

Statistical Analysis

Data obtained were entered into an Excel spreadsheet and then transferred to SPSS software (version 22; SPSS Inc, Chicago, IL) for analysis.

Results

Age of Patients

The mean age in group A (Fydrane group) is (64±3.27) compared to (65.67±3.98) in group B (Reference group) with P value (0.233), which is statistically non-significant (Table 1).

	Group A					Group B					P value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
Age	64	3.27	63	60	70	65.67	3.98	67	61	73	0.233

Table 1: Mean and SD of patients age in both groups.

Sex of Patients

Group A: 7 males (46.7%) and 8 females (53.3%)
Group B: 10 males (66.7%) and 5 females (33.3%) (Table 2).

Count		Group A		Group B		P value
		%	Count	%		
SEX	**Male**	7	46.70%	10	66.70%	0.262
	Female	8	53.30%	5	33.30%	

Table 2: Patients sex in both groups.

Safety of Fydrane on Endothelium

Comparison between the two Groups: The mean endothelial cell count preoperatively in Group A was (2407.27±332) cell/mm^2 compared to (2259.07±567.09) cell/mm^2 in Group B with P value (0.379), which is statistically non-significant. The mean endothelial cell count 3 weeks postoperatively in group A was (1807.53±550.20) cell/mm^2 compared to (1879.93±565.68) cell/mm^2 in group B with P value (0.752), which is statistically non-significant. The mean percentage of endothelia cell loss in group A is (25.74±22.7)% compared to (27.41±12.41)% in group B with value(0.595), which is statistically non-significant (Table 3).

	Group A					Group B					P value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
Preop corneal endothelia cell	2407.27	332.18	2483	1628	2915	2559.07	567.09	2626	1528	3842	0.379
After 3 weeks corneal endothelia cell	1807.53	550.2	1851	752	2861	1879.93	565.68	1809	684	2751	0.752
% of endothelia cell loss	25.74	17.62	22.27	1.85	53.81	27.49	12.41	25.99	6.48	55.24	0.595

Table 3: Mean, SD, Median, Minimum and Maximum of endothelial cell count (preoperatively and 3 weeks post operatively) and Percentage of endothelial cell loss in both groups.

Efficacy and Maintenance of Dilatation

Results in Each Group:

Group A: In Group A, all patients(100%) achieved adequate mydriasis after 30 seconds of injecting the intracameral Fydrane, with mean pupillary size (7.48±0.17)mm before capsulorhexis, and maintained adequate mydriasis throughout the surgery with mean pupillary size(7.39±0.2) mm before IOL implantation, with P value 0.058 (statistically non-significant) (Table 4).

	Group A					P value
	Mean	SD	Median	Minimum	Maximum	
Before Capsulrhexus	7.48	0.17	7.5	7.2	7.8	0.058
Before IOL Implantation	7.39	0.17	7.4	7.1	7.7	

Table 4: Mean, SD, Median, Minimum, Maximum of pupil diameter in group A.

Group B: In group B, pupillary dilatation was maintained throughout the procedure in 12 cases (80%) and intraoperative reduction in mydriasis occurs in 3 cases (20%) reaching pupil size 5.5mm before IOL implantation. The mean pupillary diameter was 7.91mm before capsulorhexis compared to 7.31mm before IOL implantation with P value 0.022 (statistically significant) (Table 5).

	Group B					P value
	Mean	SD	Median	Minimum	Maximum	
Before Capsulrhexus	7.91	0.29	7.8	7.5	8.5	0.022
Before IOL Implantation	7.31	0.96	7.6	5.5	8.2	

Table 5: Mean, SD, Median, Minimum, and Maximum of pupil diameter in group B.

Comparison between the Two Groups: Right before capsulorhexis, the mean pupil diameter in group A was (7.48±0.17) mm compared to (7.91±0.29) mm in group B, with P value (<0.001) which is statistically significant. Right before IOL implantation, the mean pupil diameter in group A was (7.39±0.2) mm compared to (7.31±0.96) mm in group B, with P value (0.0502) which is statistically non-significant (Table 6).

	Group A					Group B					P value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
Before Capsulrhexus	7.48	0.17	7.5	7.2	7.8	7.91	0.29	7.8	7.5	8.5	<0.001
Before IOL Implantation	7.39	0.17	7.4	7.1	7.7	7.31	0.96	7.6	5.5	8.2	0.0502

Table 6: Mean, SD, Median, Minimum, and Maximum and P value of pupil diameter in two steps of surgery (Before capsulorhexis and before intraocular lens (IOL) implantation in both groups.

Discussion

Fydrane is the first industrially manufactured and standardized mixture of mydriatics and anaesthetic used for injection in the anterior chamber to perform phacoemulsification. The active components, concentrations and volumes in the Fydrane formulation were based on the efficacy and safety of other IC formulations used for phacoemulsification cataract surgery [11,12].

This randomized control clinical trial studied the effect of intracameral injection of, combined mydriatic (tropicamide 0.02%, phenylephrine 0.31%) and anaethetic (lidocaine 1.0%), Fydrane on corneal endothelial cell density during phacoemulsification. This was done in comparison with standard topical regimen (reference group) in which pupillary dilatation is achieved using topical drops preoperatively.

The results of this clinical trial showed no statistical significance in the percentage of endothelial cell loss between (Fydrane group) in which mean percentage endothelial cell loss was (25.74%) and (reference group) (27.49%) with p value (0.595). The slightly higher endothelial cell loss in (reference group) is probably due to higher mean age in this group. In addition, we studied the ability of intracameral Fydrane to maintain adequate pupillary dilation throughout the phacoemulsification surgery to ensure safe surgery.

Our study showed that in Fydrane group all patients (100%) achieved adequate mydriasis after 30 seconds of injecting the intracameral drug with mean pupillary size (7.48±0.17) mm before capsulorhexis and maintained adequate mydriasis throughout the surgery with mean pupillary size (7.39±0.2) mm before IOL implantation. In Reference group, pupillary dilatation was maintained throughout the procedure in 12 cases (80%) with mean pupil size (7.9±0.3) mm. Intraoperative reduction in mydriasis occured in 3 cases (20%) reaching pupil size 5.5mm before IOL implantation which was probably caused by older patient's age patients and consequently slightly harder nucleus. As the surgical time nucleus density and ultrasound time increase for any given surgical machine they cause tissue damage and which in turn causes release of prostaglandins leading to pupillary miosis. This can be prevented by preoperative topical NSAIDs (Non-Steroidal Anti-inflammatory Drugs).

Our results are in agreement with international phase III of prospective, randomized study of Labetoulle M, et al, [11] who compared the efficacy and safety of intracameral (IC) administration of 200µL of Fydrane at the beginning of cataract surgery just after the first incision to a standard topical regimen of one drop of tropicamide 0.5% and phenylephrine 10% repeated three times (reference group). Their study was done on 555 patients. Their study indicated that IC administration of Fydrane was safe intraoperatively and postoperatively up to 1 month. Endothelial cell loss observed in the Fydrane group was similar to the reference group [7].

Also, their study showed that In the Fydrane group, the rate of capsulorhexis performed without the use of additional mydriatics (or pupil-widening maneuvers) and with a pupil size of at least 6 mm just prior to capsulorhexis was very high (96.8%) and similar to the reference group. Surgeons found that IOL implantation was less challenging in the Fydrane group compared with the reference group with more cases of IOL implantation considered 'slightly challenging' or 'challenging' in the reference group (p=0.047). Once dilated, the pupil size remained stable in the Fydrane group with a mean size of approximately 7.50 mm from viscoelastic injection until the end of surgery [7].

Our results concur with Rudy M, et al, [13] who evaluated the safety and tolerability of a single intracameral administration of Fydrane with or without rinsing in experimental study using sixty pigmented rabbits. Rabbits received 100µL or 200µL of the combination product or a placebo (sodium chloride 0.9%) by intracameral injection. For the combination product, separate groups were included with and without rinsing after administration. From day 1day to 7days assessments included general clinical and ocular observations pupil diameter measurements and corneal assessments. Their study showed that rapid mydriasis, stable 24minutes after injection and returning to baseline levels by day 1 was induced in all groups that received the combination mydriatic and anesthetic drug. Rinsing had no effect [13].

They also reported that the combination product induced no adverse effects on the anterior or posterior segment of the eye (i.e., no increased corneal thickness and endothelial cell loss, no abnormalities in electroretinogram ERG). No toxic effects of the products were found on histological evaluation. So they reached a conclusion that the combination mydriatic and anesthetic drug administered to pigmented rabbits as a single intracameral injection at volumes of 100 µL and 200 µL was well tolerated with no ocular adverse effects and no effect on the corneal endothelium [13].

Ajay K, et al. [14] showed similar results to our study when they assessed the efficacy and safety of intracameral mydriatic solution containing 0.5% lignocaine and 0.001% epinephrine injected immediately after first entry into the anterior chamber (AC) as compared to preoperative topical

mydriatics in patients undergoing manual small incision cataract surgery (MSICS) under peribulbar anesthesia in a study on 127 patients. Pupil sizes were measured serially, at six different junctures during surgery.

Their results showed Mean pupil size just before peribulbar block was 7.3 mm in topical group and 3.3mm in intracameral group (P<0.001). Mean pupil size in intracameral group increased to 7.3mm 30 s after injecting intracameral dilating solution. Mean pupil size in both groups progressively reduced reaching 5.5mm (topical group) and 6.2mm (intracameral group) just before intraocular lens implantation (P=0.001) and measured 5.1mm and 5.5mm respectively at the end of surgery (P=0.048). On first postoperative day there was no significant difference in distribution of corneal edema scores AC inflammation scores, and in median log MAR visual acuity between the two groups [14].

Chiambaretta F, et al. [15] also showed similar results to ours when they compared the effect of intracameral injection of combination of 2 mydriatics and 1 anesthetic to a standard topical regimen for cataract surgery in a prospective case series in which pupil size measurements were performed in 2 randomized studies (phase 2 and phase 3) which comprised 139 patients and 591 patients, respectively. After intracameral combination administration 95% of the pupil dilation was achieved within a mean of 28.6 seconds±4.6 (SD). At the beginning of capsulorhexis creation the mean pupil diameter was larger than 7.0mm in both groups. The intraoperative pupil diameter remained stable in the intracameral combination group and decreased in the topical group. The mean change in pupil size just before capsulorhexis to the end of surgery (just before cefuroxime injection) was 0.22±0.72mm and 1.67±0.98mm respectively. No clinically significant change in pupil diameter (change<1.0mm) occurred in the majority of the intracameral combination group (89.3%) compared with the topical group (26.8%) [15].

Gupta SK, et al. [16] also showed matching results with ours when they evaluated the role of intracameral irrigating solution (0.5% lignocaine+0.001% epinephrine) in initiating and maintaining the pupillary mydriasis during phacoemulsification and observe the effect of surgical time, nucleus density and ultrasound time on mydriasis during the procedure in a a prospective interventional case series on thirty patients underwent phacoemulsification under topical anesthesia. The pupil size increased from 2.1mm (Range 2-3.5mm SD±0.32) to 6.9 mm (range 5-9mm SD±1.02) in 30 seconds time after intracameral mydriatic solution delivery and was 7.0mm at the end of surgery. Duration of surgery grade of nucleus and ultrasound time had statistically insignificant effect on mydriasis [16].

Study Limitations

A drawback of our study is the small number of cases included. It does not study the other possible ocular side effects of Fydrane like posterior segment affection e.g. macular edema. It does not study the possible systemic adverse effects e.g. cardiovascular. This trial shows a 3weeks outcome which may not necessarily be indicative of longer-term outcomes. However, the aim of this study was to evaluate the safety of the Fydrane on endothelium and its mydriatic effect to determine its suitability for cataract surgery.

Based on this objective, we believe the 3 weeks period is appropriate for this evaluation because

- Postoperative follow-up by most cataract surgeons is 1 month;
- The potentially severe adverse effects of Fydrane (mostly toxicity on endothelial cells) were typically expected within days to weeks postoperatively;
- The long-term adverse effects of cataract surgery (i.e., retinal breaks and detachments) are related to the surgical procedure rather than to the products used preoperatively or intraoperatively. We recommend increasing the sample size and increasing the period of post-operative follow up to detect any other possible local and/or systemic adverse effects.

Summary and Conclusion

Fydrane is the first commercially available intracameral mydriatic and anaesthetic mixture licensed for use during cataract surgery; it is comprised of a standardized combination of tropicamide 0.02%, phenylephrine 0.31%, and lidocaine 1.0%. First launched in Italy in 2016 this product is currently licensed for use in all 27 countries in the European Union.

This study showed that intracameral injection of Fydrane is safe on corneal endothelium, as no statistically significant difference in the percentage of endothelial cell loss was found between Fydrane and standard topical regimen groups. It also showed that Fydrane is effective in maintaining pupillary dilatation throughout the surgery, avoiding intraoperative meiosis which may occur with the traditional pupil dilatation using topical mydriatics preoperatively.

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