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# Cardiovascular effects of diluted intracameral combination of 0.02% tropicamide, 0.31% phenylephrine, and 1% lidocaine during phacoemulsification to manage intraoperative miosis

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## Abstract:

**PURPOSE:** Intracameral mydriatic agents (ICMAs) are replacing the conventional method of topical mydriasis for its fast action and no need for repeated instillation before cataract surgery. Its application for the management of intraoperative miosis needs to be studied with different doses of mydriatic agent. The objective of the study is to study cardiovascular effects of diluted intracameral combination of 0.02% tropicamide, 0.31% phenylephrine, and 1% lidocaine during phacoemulsification to manage intraoperative miosis.

**MATERIALS AND METHODS:** The study was conducted at Mojiram Lions Eye Hospital Akbarpur Majra village, Palla Bakhtawarpur Road, Delhi, during the year 2021–2022 after taking approval from the Ethical Committee of the hospital. Patients undergoing cataract surgery who were not dilated adequately during the preoperative period or developed intraoperative miosis were managed by injecting diluted intracameral combination of 0.02% tropicamide, 0.31% phenylephrine, and 1% lidocaine (phenocaine plus). 0.5 ml of phenocaine plus was diluted with 1.5 ml of ringer lactate solution and 0.50 ml of this solution was injected intracameral and its effect on pulse rate, blood pressure (BP), and oxygen saturation were monitored continuously on pulse oximeter.

**RESULTS:** There was no statistically significant effect of diluted ICMA (Phenocaine Plus) on diastolic BP and oxygen saturation. However, systolic BP showed a little change from mean of 133.78 (standard deviation [SD] = 16.04) mmHg to 133.92 (SD = 15.33) mmHg which was statistically significant but clinically not significant. Pulse rate increased slightly from mean 76.46 per minutes (SD = 15.14) to 79.40 (SD = 14.95) at 10 s and 76.49 (SD = 15.15) at 60 s. The difference was again statistically significant but clinically insignificant.

**CONCLUSION:** Low concentration of intracameral combination of 0.02% tropicamide, 0.31% phenylephrine, and 1% lidocaine is a very safe and effective method for the management of intraoperative miosis.

## Keywords:

Cardiovascular effects, intracameral mydriatic, intraoperative miosis, phacoemulsification

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## Introduction

Cataract is one of the leading causes of blindness. Phacoemulsification with intraocular lens (IOL) implantation is the standard procedure of treatment.<sup>[1]</sup> Cataract surgery is reported to be the second most common ocular surgery after intra-vitreous injections.<sup>[2]</sup> For satisfactory outcome of phacoemulsification technique, adequate pupillary dilatation before surgery and its maintenance during surgery is a must.<sup>[1-3]</sup> Similarly, adequate anesthesia during surgery is also a must for rewarding outcomes.<sup>[4]</sup> Various methods of preoperative pupillary dilatation have been in practice. Topical use of 0.8% tropicamide and 5% phenylephrine is one of the most accepted methods. However, poor drug penetration, hence poor bio-availability, prolonged time required to achieve adequate pupillary dilatation, need for repeat administration, and corneal and systemic toxicity of drugs are the limitations of this conventional technique. Since 2003, intracameral phenylephrine has been used as an alternative to topical mydriatics with a reportedly good safety profile.<sup>[5-7]</sup>

Peribulbar anesthesia, retrobulbar anesthesia with facial block, and topical anesthesia are the various means of making the surgical experience painless. Peribulbar and retrobulbar anesthesia are associated with fatal complications such as globe perforation and retrobulbar hemorrhage.<sup>[8]</sup> Topical anesthesia is devoid of these complications. However, to make the surgical experience absolutely painless, intracameral lidocaine is used frequently. Similarly, to manage intraoperative miosis, combination of tropicamide/phenylephrine/lidocaine is also in practice.<sup>[4]</sup>

Phenylephrine hydrochloride belongs to a group of drugs called sympathomimetics. It is different from epinephrine by the absence of hydroxyl group in the position 4 of benzene ring. It is used as a mydriatic without cycloplegia as it does not paralyze ciliary muscles.<sup>[1]</sup> Its action is mainly on the alpha-adrenergic receptors of dilator pupillae muscle with minimal effects on the beta-receptors. It stimulates the release of norepinephrine. It has a direct effect on nerve receptors, mainly located on the pupillary dilator muscles.<sup>[9]</sup>

Tropicamide is a muscarinic receptor antagonist. It belongs to the class of anticholinergics. It is used to induce dilatation of pupil with minimal paresis of ciliary muscles.<sup>[9]</sup>

Lidocaine is used as a local anesthetic drug. Case reports of this drug being injected intracameral inadvertently with no ill effects lead to the idea of its being used as intracameral mydriatic and anesthetic agent. It also helps dilate the pupil by its direct relaxing action on sphincter

pupillae.<sup>[7,10,11]</sup> Endothelial cell loss after the use of this drug during cataract surgery was comparable to a normal cataract surgery.<sup>[11-13]</sup> Lidocaine inhibits propagation of sensory nerve impulse to the brain and thus is helpful for relieving pain during topical phacoemulsification. The application of lidocaine gel over the cornea is a common practice to achieve anesthesia. However, recent studies have reported that concentrations higher than 1% can cause damage to corneal epithelial cells.<sup>[3]</sup> Deeks concluded in his studies that plasma concentration of tropicamide, phenylephrine, and lidocaine was below detectable limits after the use of intracameral injection hence no chances of systemic side effects. This is in contrast to the peribulbar/retrobulbar anesthesia where 5 ml of 2% lidocaine used led to remarkable serum concentrations of this drug.<sup>[3]</sup>

Dark iris population requires higher concentration of mydriatic drugs that increase the chances of ocular and systemic side effects. Majority of the Indian population has dark-colored irides, grade 4 or 5 of iris color.<sup>[3]</sup>

Topical application of lidocaine before instillation of tropicamide and phenylephrine enhances pupillary dilatation and the time required to dilate the pupil is greatly decreased. This is because lidocaine causes corneal epithelial edema and increases the penetration of other drugs.<sup>[3]</sup>

Topical and intracameral use of combination of 0.02% tropicamide, 0.31% phenylephrine, and 1% lidocaine have been well documented in various publications as a tool to dilate the pupil. The first fixed-dose mydriatic combination approved for intracameral use was tropicamide 0.02%, phenylephrine 0.31%, and lidocaine 1% injectable solution (Mydrane<sup>®</sup>). In India, it was made available in the name of Phenocaine Plus.<sup>[3]</sup>

Certain conditions such as long-standing diabetes, Ch. Uveitis, long-term use of pilocarpine for the treatment of angle closure glaucoma, and old age lead to nondilatation of pupil and are causes of intra-operative miosis. Diabetes causes neuropathy and alterations in vasculature which makes pupil resistant to dilatation. A similar presence of posterior synechiae in Ch. Uveitis compromises pupillary dilatation. Surgery becomes very difficult if adequate intraoperative mydriasis is not maintained. Application of iris hooks and rings has been tried. They are excellent ways for mechanical dilatation of pupil but pupil becomes permanently deformed in some cases due to mechanical damage caused to sphincter pupillae.<sup>[14-20]</sup>

Diluted form of injection adrenaline has been widely used to counter the intraoperative miosis. However, rise in blood pressure (BP), pulse rate, and risk of cardiac ischemia are the issues of concern.<sup>[18]</sup>

Because combination of tropicamide, 0.02% phenylephrine 0.31%, and lidocaine 1% injectable solution is being used more and more nowadays after recent studies, it becomes essential to try different concentrations of the drug to evaluate its efficacy and side effects. We tried diluted concentration of the above-mentioned combination to counter intraoperative miosis and studied its effect on pulse rate, BP, and oxygen saturation.

### Aims and objectives

1. To evaluate cardiovascular effects (heart rate and BP) of the combination of low concentration, intracameral administration of tropicamide, phenylephrine, and lidocaine during phacoemulsification for the management of intra-operative miosis
2. To evaluate the effects of combination of low concentration, intracameral administration of tropicamide, phenylephrine, and lidocaine on oxygen saturation during phacoemulsification for the management of intraoperative miosis.

### Review of literature

Gills *et al.*<sup>[11]</sup> conducted a study on 183 patients undergoing suture-less small incision cataract surgery. In this prospective controlled study, 0.1 ml unpreserved lignocaine (1%) was injected intracameral 1 min before starting surgery. Discomfort felt by patient during cataract surgery was assessed using a predefined uniform pain scale. The results were compared with another group who received Balanced salt solution (BSS) intracameral as placebo. It was concluded that intracameral lidocaine was very much helpful in reducing the intraoperative discomfort during cataract surgery. There was no significant adverse effect on endothelial cell count. Carino *et al.* also had similar observation in their study conducted on 60 eyes of 59 patients. Patient satisfaction level, surgeon satisfaction level, endothelial cell count, and rate of potential visual acuity recovery were much better with topical tetracaine (0.5%) and intracameral lidocaine (1%) when compared with a placebo therapy.

Carino *et al.*<sup>[12]</sup> conducted a study on 59 patients planned for phacoemulsification. Patients were divided into two groups. Control group received topical tetracaine and intracameral BSS and the study group received topical tetracaine plus IC lidocaine. Patient and surgeon satisfaction levels were measured with five-point satisfaction scale, endothelial cell count, and best-corrected visual acuity were measured. It was concluded that topical tetracaine and intracameral lidocaine combination was very effective in achieving anesthesia for phacoemulsification with foldable IOL implantation.

Ghose *et al.*<sup>[15]</sup> conducted a study on 60 eyes of thirty patients with dark irides in two phases. In phase 1, he

studied the effect whether preinstallation of lidocaine potentiates mydriasis. He found that mydriasis was significantly more in study group as compared to placebo group. In the second phase, it was concluded that epithelial edema caused by preinstillation of lidocaine increases penetration of mydriatic drugs and thus making them more bioavailable leading to enhanced mydriasis.

Nuzzi *et al.*<sup>[16]</sup> demonstrated safety and efficacy of mydrane in complicated cases of phacoemulsification. The study was conducted on 125 patients. It was concluded that 99.2% of patients who received intracameral Mydrane achieved acceptable mydriasis (>6 mm) and the surgery could be completed without additional mydriatics.

### Materials and Methods

Patients being planned for phacoemulsification with IOL implantation aged 30–80 years were dilated with 5% phenylephrine and 0.8% tropicamide combination before surgery. Those who were not dilated adequately with this combination and/or who developed intraoperative miosis were dilated with low concentration of combination of 0.02% tropicamide, 0.31% of phenylephrine, and 1% lidocaine (Phenocaine Plus), intracameral preparation during surgery. One hundred and fifty-seven eyes of 157 such patients were chosen for the study. The low-concentration drug was prepared by taking 0.50 ml of the drug in 2 ml syringe and filling it up to 2 ml mark with fresh ringer lactate solution. 0.50 ml of this preparation was injected intracameral after recording BP, pulse rate, and oxygen saturation on pulse oximeter. The pulse rate was recorded from the cardiac monitor before injection of intracameral mydriatic agents (ICMAs), at 10 s and 60 s after ICMA injection. The oxygen saturation was also recorded before injection of ICMA and repeated at 10 s and 60 s after ICMA injection. BP was recorded before the injection of ICMA and after 1 min or more postinjection using the noninvasive BP cuff. At 60 s postinjection, pulse rate and oxygen saturation returned to normal and the patient was clinically stable.

The study was performed in compliance with the ethical principles having their origins in the Declaration of Helsinki (2004) regarding biomedical research on human patients and the Indian Council of Biomedical Research Guidelines for studies on humans 2017. The study complied with applicable regulatory requirements and in accordance with Good Clinical Practice. The study was conducted at Mojiram Lions Eye Hospital Akbarpur Majra Village Palla-Bakhtawarpur Road Delhi. The study was approved by the Institutional Review Board of Mojiram Lions Eye Hospital, Akbarpur Majra, Delhi, India. (approval number: MLEH/Ophthal/Corrs/2021-22/01). Written and oral information was

provided to each patient and a signed written consent was taken before the patient was enrolled.

### Exclusion criteria

Patients older than 80 years, suffering from hypertension and ischemic heart disease, and who were not willing to give consent were not included in the study. Patients having any known history of allergy to any of the drugs being used were excluded from the study.

### Sample size considerations

Assuming the population size to be infinite and the population proportion at 0.5, the highest variance, with the margin of error of 8% with a confidence level of 0.05, we got a sample size of 151. Since no other study was available with a diluted lower concentration ICMA for this exploratory research. Data were analyzed using the SPSS Statistics for Windows, version 23.0 (Armonk, NY, USA: IBM Corp). Descriptive data of variables were presented and repeated measures statistical analysis were performed for comparisons.

## Results

The mean age of the sample was 57.87 (standard deviation [SD] = 11.49, skewness = -0.835, and kurtosis = 0.194). Males (54.4%) outnumbered females (45.6%).

The cardiovascular parameters recorded were pulse rate and BP. The pulse rate before the surgery ranged from 49 to 122, with a mean of 76.46 (SD = 15.14). At 10 s from injection of the ICMA, it ranged from 53 to 125 with a mean pulse rate of 79.40 (SD = 14.95). At 60 s after the injection of the ICMA, it ranged from 49 to 122 with a mean pulse rate of 76.49 (SD = 15.15). The difference was statistically significant (Kendall's  $W = 0.897$ ,  $P = 0.000$ ) when repeated measures Friedman test were employed.

The systolic BP went up from the mean of 133.78 (SD = 16.04) mm of Hg to 133.92 (SD = 15.33) mm of Hg ( $Z = -2.376$ ,  $P = 0.018$ , Wilcoxon signed ranks test) which though statistically significant was clinically not significant. The diastolic BP postoperatively with a mean of 81.03 (SD = 7.46) mm of Hg was not significantly different from the preoperative levels of 80.42 (SD = 9.84) mm of Hg ( $Z = -0.777$ ,  $P = 0.437$ , Wilcoxon signed-ranks test).

The oxygen saturation varied from 96% to 100% preoperatively with a mean of 99.07 (SD = 0.885, skewness = -0.812, Kurtosis = 0.584) to mean of 99.07 (SD = 0.885, skewness = -0.812, Kurtosis = 0.584) at 10 s after injection to mean of 99.08 (SD = 0.888, skewness

= -0.818, Kurtosis = 0.586) at 1 min or more after ICMA. The difference was not statistically significant (Kendall's  $W = 0.006$ ,  $P = 0.392$ , Friedman's test).

## Discussion

ICMAs have gained acceptance in phacoemulsification. Mydrane/Phenocaine Plus is a fixed dose combination containing 0.2 mg/ml of tropicamide, 3.1 mg/ml of phenylephrine hydrochloride and 10 mg/ml of lidocaine hydrochloride with sodium being the only excipient with known effect for injection in the intracameral space. A single dose of 0.2 ml solution contains 0.04 mg of tropicamide, 0.62 mg of phenylephrine hydrochloride, and 2 mg of lidocaine hydrochloride. It has been marketed for surgical use in patients demonstrating a satisfactory pupil dilation with topical mydriatic therapy at pre-operative assessment. Phacoemulsification is practiced as day care surgery and the patients come from residences for the surgery. The injection can be used for intraoperative mydriasis maintenance or for patients who may not have shown drug compliance prior to surgery. A 0.2 ml of phenocaine is recommended to be injected at the start of the surgical procedure by the intracameral route. It can also be used as adjunct in patients demonstrating inadequate pupillary dilatation during phacoemulsification, especially in conditions prone to poor mydriasis like pseudoexfoliation, chronic uveitis, prolonged surgery, floppy iris, etc.<sup>[21-23]</sup>

In our study, the pulse rate rose from a mean of 76.46 (SD = 15.14) beats per minute before the surgery to a mean pulse rate of 79.40 (SD = 14.95) at 10 s from injection of the ICMA settling down to a mean pulse rate of 76.49 (SD = 15.15) at 60 s after the injection of the ICMA (Kendall's  $W = 0.897$ ,  $P = 0.000$ , Friedman test). In our study, there was a transient increase in the pulse rate with intracameral phenocaine injection which could not be demonstrated at 1 min from ICMA injection. This was different from the findings of Farahat *et al.* who reported no difference in the mean of pulse rate of  $71.08 \pm 4.59$  bpm postintracameral epinephrine (analysis of variance test,  $P = 0.863$ ).<sup>[24]</sup> However, they have not specified the time intervals at which they recorded the pulse rate. Morgado *et al.* have also reported that the intracameral mydriatics have a good profile for the cardiovascular system. Stavert *et al.* in their meta-analysis of eight randomized controlled trials combining the data of 916 participants reported that there was no effect on BP or heart rate at 20–30 min and 60 min or longer after administration of topical phenylephrine, 2.5%. No study was available for diluted mydriatic mixture as an adjunct to peribulbar anesthesia. The change appears to be transient and therefore requires larger studies with a more continuous sampling of the parameters. As a result,

the authors suggest the use of a diluted intracameral mixture for routine surgery where the mixture is being used only as an adjunct for mydriasis maintenance.<sup>[25,26]</sup>

The oxygen saturation in our study was largely unchanged with a mean of 99.07 (SD = 0.885, skewness = -0.812, Kurtosis = 0.584) preoperatively to mean of 99.07 (SD = 0.885, skewness = -0.812, kurtosis = 0.584) at 10 s after injection and a mean of 99.08 (SD = 0.888, skewness = -0.818, and kurtosis = 0.586) at 1 min or more after ICMA. On repeated measures analysis, this difference was not statistically significant (Kendall's W = 0.006,  $P = 0.392$ , Friedman's test). There are no other studies available on the effect of intracameral mydriatic injection on oxygen saturation. This is in line with the safety profile of the agent and it is a reassurance in these post-COVID era when long COVID has started emerging as a problem in some patients recovered from COVID. This also rules out any interactions among the drugs that could affect the respiratory system stability of the patients undergoing treatment with this agent.

The systolic BP in our group went up from the mean of 133.78 (SD = 16.04) mm of Hg preoperatively to 133.92 (SD = 15.33) mm of Hg (Z = -2.376,  $P = 0.018$ , Wilcoxon signed-ranks test) at 1 min or more after the injection of ICMA which though statistically significant was clinically not significant. In the previous studies by Farahat *et al.*, the mean of preintracameral epinephrine systolic BP was  $126.83 \pm 7.21$  mm of Hg which was not significantly different from the mean of systolic BP postintracameral epinephrine of  $127.80 \pm 7.67$  mm of Hg ( $P = 0.353$ ). This effect may be due to race differences between those studies and our population. It may be an artifact related to the small sample size and larger studies will be necessary to confirm the results of the present study. Other studies have also focused on BP after several minutes and not reported significant differences between pre- and postinjection systolic or mean BP. Stavert *et al.* in their meta-analysis of 916 participants reported that 10% phenylephrine topically increased BP at 5 and 10 min (mean difference for both, +15 mm Hg; 95% confidence interval, 11.94–18.54;  $P < 0.001$ ) but decreased at 20–30 min and 60 min or longer with no changes detected against baseline. Lower concentration of topical 2.5% phenylephrine did not affect BP at 20 to 30 min and 60 min or longer after administration. Since the cataract surgery does not last that long at our center or for most surgeons in general, we looked at more real life time spans. The difference in concentration has an effect on the response to the phenylephrine and this suggests that the intracameral drug has a profile closer to a 10% topical concentration rather than 2.5% concentration.

In our study, the diastolic BP postoperatively with a mean of 81.03 (SD = 7.46) mm of Hg was not significantly

different from the preoperative levels of 80.42 (SD = 9.84) mm of Hg (Z = -0.777,  $P = 0.437$ , Wilcoxon signed ranks test). The previous studies have reported similar results. Farahat *et al.* reported that the mean of preintracameral epinephrine diastolic BP of  $75.83 \pm 5.52$  mm of Hg was not significantly different from the mean of diastolic BP post intracameral epinephrine of  $76.13 \pm 5.49$  mm of Hg ( $P = 0.414$ ). The lack of effect on the diastolic BP compared to the elevation can be explained by selective activation of beta receptors at lower concentrations and of both alpha and beta receptors at higher concentrations. The beta receptors cause a vasodilatation while the combined effect results in the increase of heart rate and the vasoconstriction. It may, however, be due to a small population size and larger studies would be required to ensure that the results become more generalizable.

## Conclusion

ICMAs have a good safety profile and are becoming acceptable for drop-less cataract surgery. Even in lower concentrations than those used clinically, they have a transient effect on the heart rate and systolic pressure. This should be borne in mind when taking up surgery using ICMA in the geriatric population with co-existing cardiovascular comorbidity. The effect is seen in the Indian population when lower concentrations were used than in the western literature. The effects are transient and do not mandate any special precautions. The authors advocate judicious use in patients with cardiovascular comorbidity.

## Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Nil.

## Conflicts of interest

The author declares that there are no conflicts of interest in this paper.

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