Safety of tropicamide and phenylephrine in pupillary mydriasis for cataract surgery

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Abstract:

PURPOSE: A prospective study to evaluate the adverse cardiovascular effects of topical phenylephrine and tropicamide used for pupillary mydriasis before cataract surgery.

METHODS: A total of 517 consecutive eyes in 517 patients subjected to routine 0.8% tropicamide and 5% phenylephrine eye drops before undergoing cataract surgery (phacoemulsification and manual small-incision surgery) under local or topical anesthesia in a medical college hospital were analyzed.

RESULTS: No untoward cardiovascular effects were seen. The increase in blood pressure after 0.8% tropicamide and 5% phenylephrine eye drops was statistically significant, but it was not relevant as it was within clinically permissible limits.

CONCLUSION: The combination of 0.8% tropicamide and 5% phenylephrine eye drops is a safe and effective option for pupillary mydriasis before cataract surgery.

Keywords: Blood pressure, mydriasis, phacoemulsification, phenylephrine, tropicamide

INTRODUCTION

Cataract surgery requires a good pupillary dilatation for better access to the lens surface, and the use of tropicamide and phenylephrine is a popular combination for this purpose. Tropicamide is a short-acting anticholinergic agent used as a mydriatic and cycloplegic. The drug effect begins within 15–20 min of instillation and lasts for 4–6 h. However, tropicamide fails to give good pupillary dilatation when used alone, especially in patients with diabetes mellitus, dark-pigmented irides, and in the elderly. Phenylephrine is a direct-acting sympathomimetic agent used topically in the eye as a mydriatic, available in concentrations up to 10%.

Although either of these two drugs alone produces adequate mydriasis, the combination produces maximal mydriasis that is resistant to the intense light of the operating microscope.

Although topical ophthalmic preparations are safe to use, they may cause unwanted systemic side effects due to systemic absorption through the cornea, conjunctiva, and nasal mucosa through the lacrimal sac. There are several case reports in the literature of an episodic rise in blood pressure and arrhythmias following the use of phenylephrine. Chin et al. reported a significant hypertensive rise in blood pressure in 89 consecutive cases of uncomplicated cataract surgery. Malhotra et al. in their double-masked randomized study of 54 consecutive patients undergoing routine local anesthetic cataract extraction found no sustained changes in blood pressure or heart rate (HR) after instillation of either 2.5% or 10% topical aqueous phenylephrine. Kenawy and Jabir, in their study on 2.5% and 10% phenylephrine in phacoemulsification under topical anesthesia, showed that patients subjected to either dose experienced a rise in systolic blood pressure (SBP) that was statistically significant. The upper limit of safety for intravenous administration of phenylephrine was...
shown to be 1.5 mg,[1] and Kumar et al.[2] found phenylephrine plasma levels after the administration of a topical 10% solution to be 1.842–11.526 ng/ml after 20 min.

Recent studies have shown pulse pressure (PP) to be a predictor of coronary events and mean arterial pressure (MAP) to be a better predictor of stroke and cerebrovascular events.[7,8] Therefore, in addition to systolic and diastolic pressures, the present study utilized HR, MAP, and PP to study the cardiovascular effects of a combination of tropicamide and phenylephrine.

Against this background, the purpose of this study was to evaluate the effect of phenylephrine eye drops on the cardiovascular system in normotensive individuals undergoing cataract surgery with local or topical anesthesia.

**Methods**

This prospective study was carried out on 517 patients undergoing cataract surgery (phacoemulsification or manual small-incision surgery) with local anesthesia from August 1, 2018, to April 30, 2019, at a medical college hospital in Hyderabad. Patients with hypertension and coronary artery disease were excluded from participation in the study. Furthermore, patients with any history of previous ocular surgery or using any other eye drops were also excluded from the study. A commercially available combination of 0.8% w/v tropicamide and 5% w/v phenylephrine was used for dilatation. One drop was instilled in the lower conjunctival fornix every 15 min, starting 1 h before scheduled cataract surgery. Only three instillations were done. Topical anesthetic agent was not included in the regimen. A drop of nonsteroidal anti-inflammatory agent (flurbiprofen, 0.03% w/v) was instilled after the mydriatic drops. This does not possess mydriatic effects, and it does not affect the results of the study, but it helps to maintain pupillary dilatation during surgery. There are no sedatives given in the preoperative regimen. Baseline blood pressure and HR were recorded and then also at the following time points after tropicamide and phenylephrine eye drop instillation: 5, 10, 15, and 30 min; 1, 2, and 3 h. No more additional drops were given after the third eye drop instillation to avoid any adverse effect on the outcome from a cumulative effect of systemic absorption of phenylephrine.

**Statistical analysis**

The numerical data were displayed by mean and standard deviation and categorical data as ratio. The hemodynamic parameters measured at different timings were measured by analysis of covariance using the generalized linear model, followed by Bonferroni post hoc tests. The Chi-square test was performed for categorical data. The \( P < 0.05 \) was considered statistically significant.

**Results**

Taking into consideration age, gender, height, and weight, the demographic data were found to be normally distributed using the Shapiro–Wilks W-test. The demographic data from the patients are summarized in Table 1.

Patients were middle aged and elderly with a female preponderance. Hypertensive patients were excluded but the group included diabetics with good glycemic control.

The SBP showed an increase of 5 mmHg between baseline and the final reading at 3 h, and there were no wide variations in recordings during the entire period [Figure 1].

The diastolic blood pressure (DBP) was also stable throughout the entire period, with a difference of only 3 mmHg between baseline and the final reading [Figure 2].

HR showed an initial spike that later stabilized throughout the entire observation period [Figure 3]. Anxiety may be a factor for this very early spike.

MAP and PP were stable throughout, with very little variation in recordings [Figures 4 and 5].

All the hemodynamic parameters were maintained within clinically permissible limits throughout the study period. The differences in the means of baseline and final readings appear to be statistically significant, but they were not clinically significant [Tables 2 and 3].

**Discussion**

A combination of 0.8% tropicamide and 5% phenylephrine is commonly used for pupillary mydriasis before fundus

![Figure 1: Mean systolic blood pressure across time. SBP = Systolic blood pressure; SBP BS at baseline, SBP 5 at 5 min, 10 M at 10 min, 15 M at 15 min, SBP 20M at 20 min, SBP 30M at 30 min, SBP 1H at 1 h, SBP 2H at 2 h, SBP 3H at 3 h](image)

| Table 1: Demographic data (mean±standard deviation) |
|----------------------------------------------------|
| Characteristics | Baseline Values |
|-----------------|-----------------|
| Age (years)     | 60.49±30.7      |
| Gender (male: female) | 39:61     |
| Weight (kg)     | 53.7±12.5       |
| Height (cm)     | 153.57±8.6      |
examination and cataract and vitreoretinal surgery; tropicamide and phenylephrine at lesser concentrations are not very effective. In Caucasians, 2.5% is found to be as effective as 10% phenylephrine for producing mydriasis, with fewer side effects. There are reports indicating that, in dark-pigmented irides, 10% is more effective than 2.5% phenylephrine in maintaining mydriasis during cataract surgery. There were no studies reported in the literature search with a large enough sample size to demonstrate the efficacy and safety of 5% phenylephrine in maintaining mydriasis. The present study has a large sample size of 517 patients, and this gives it authenticity.

The results showed a wide range of baseline readings for several hemodynamic factors – HR, systolic and DBP, PP, and MAP – which is understandable, given the wide age variation of the patients. This study does not find any adverse effect of 5% phenylephrine on blood pressure or HR. All the parameters – systolic and DBP, MAP, and HR – except PP show a statistically significant difference between baseline and the final reading at 3 h, but these are not clinically significant enough to impact the cardiovascular status. Sedatives were excluded from the preoperative regimen because they are known to mask the effects of anxiety and the systemic effects of mydriatics on blood pressure and HR. Only three instillations were made, at 15-min intervals, to prevent cumulative effects of phenylephrine due to systemic absorption. Maximal plasma levels of phenylephrine are achieved after 20 min.

Previous studies on the cardiovascular effects of phenylephrine eye drops have reported conflicting results. Samantary and Thomas observed a rise in blood pressure in all of their sixty cases, and there were reports of acute episodes of systemic hypertension after topical use of 10% phenylephrine. The only randomized controlled trial to study the effects of 10% phenylephrine eye drops on blood pressure and HR reported no effect, and a systematic literature review and meta-analysis by Stavert et al. found that the hazardous effect of 10% phenylephrine reported in the literature may have been overstated.

In the present study, the authors have shown that, although the differences between baseline and the final reading of blood pressure and HR were statistically significant, they were not clinically significant. Almost all the mean blood pressure

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**Figure 2:** Mean diastolic blood pressure across time

**Figure 3:** Mean heart rate across time

**Figure 4:** Mean arterial pressure across time

**Figure 5:** Mean pulse pressure across time
Table 2: Mean±standard deviation values for blood pressure (mmHg) and heart rate (bpm) at all time points (n=517)

|        | SBP       | DBP       | HR         | PP         | MAP       |
|--------|-----------|-----------|------------|------------|-----------|
| Baseline | 123±18.9  | 73.8±10.8 | 74.9±13.5  | 47.7±12.5  | 87.4±13.4 |
| 5 min   | 124±19.1  | 75.1±11.1 | 77.7±13.7  | 47.8±12.4  | 89.6±14.1 |
| 10 min  | 122.8±19.4| 74.0±10.8 | 76.9±13.9  | 47.2±13.6  | 88.4±13.7 |
| 15 min  | 123.1±18.4| 73.8±10.7 | 76.2±13.5  | 47.7±12.8  | 87.7±13.1 |
| 20 min  | 125.2±46.2| 73.9±10.7 | 75.8±13.3  | 49.4±45.0  | 88.0±13.5 |
| 30 min  | 123.3±18.3| 74.2±10.6 | 75.7±13.2  | 47.3±12.9  | 87.7±12.9 |
| 1 h     | 125.6±20.1| 75.0±11.25| 74.8±13.5  | 48.4±14.6  | 88.3±14.0 |
| 2 h     | 127.4±19.0| 75.3±10.9 | 75.2±13.3  | 49.8±15.2  | 88.0±12.7 |
| 3 h     | 127.6±18.1| 76.6±10.8 | 76.0±13.6  | 49.2±14.0  | 89.5±12.6 |

SBP=Systolic blood pressure; DBP=Diastolic blood pressure; HR=Heart rate; PP=Pulse pressure; MAP=Mean arterial pressure

Table 3: Mean±standard deviation values for blood pressure (mmHg) and heart rate (bpm) at baseline and at 3 h

|                        | Baseline reading | Final reading | P      |
|------------------------|------------------|---------------|--------|
| Systolic BP (mmHg)     | 123±18.9         | 127±18.1      | 0.00096|
| Diastolic BP (mmHg)    | 73.8±10.8        | 76.6±10.8     | 0.0025 |
| HR (bpm)               | 74.9±13.5        | 76.0±13.6     | 0.01   |
| PP (mmHg)              | 47.7±12.5        | 49.2±14.0     | 0.25   |
| MAP (mmHg)             | 87.4±13.4        | 89.5±12.6     | 0.07   |

BP=Blood pressure; HR=Heart rate; PP=Pulse pressure; MAP=Mean arterial pressure

Changes observed between baseline and the final reading were <10 mmHg. In one study, a SBP variation of 15 mmHg or less was defined as normal, and an increase of more than this was associated with an increased prevalence of coronary artery disease.[15] Thus, a small blood pressure change of <10 mmHg is of no clinical significance.

**CONCLUSION**

The authors have demonstrated that the combination of 0.8% tropicamide and 5% phenylephrine is a safe and effective option for pupillary mydriasis in patients with dark-pigmented irides, but no history of hypertension or coronary artery disease, undergoing ocular surgery. However, patients should be monitored throughout surgery and for a few hours postoperatively to prevent individual instances of adverse reactions to phenylephrine. Furthermore, multiple and frequent instillations of drops should be avoided to prevent any untoward cumulative dosage effects in the blood due to systemic absorption.

This study confirms that 5% phenylephrine is a safe drug if applied topically.

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**Conflicts of interest**

There are no conflicts of interest.

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