

Original Investigation

Cardiovascular Adverse Effects of Phenylephrine Eyedrops

A Systematic Review and Meta-analysis

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IMPORTANCE Topical phenylephrine hydrochloride is routinely administered with few safety precautions, but evidence regarding its systemic safety to date is controversial. As even short-term variations in 24-hour blood pressure (BP) and heart rate (HR) can adversely affect cardiovascular health, better evidence on phenylephrine's effects on HR and BP is required.

OBJECTIVE To perform a meta-analysis of available evidence regarding cardiovascular adverse effects of topical phenylephrine.

DATA SOURCES PubMed, MEDLINE, and the Cochrane Database of Systematic Reviews and Clinical Trials were searched for relevant literature from January 1, 1970, to January 1, 2014, using a combination of the following search terms: *topical, ocular, ophthalmic, phenylephrine, tropicamide, cardiovascular effect, side effect, blood pressure, heart rate, mydriatic, and eye drops*. A total of 70 articles related to the topic were identified and all full texts were retrieved.

STUDY SELECTION Randomized clinical trials reporting change in BP and HR for adults were included in this review. All studies reporting results for neonates or infants, not reporting standard deviations, or not specifying the time of measurement or the concentration of phenylephrine used were excluded.

DATA EXTRACTION AND SYNTHESIS Data from randomized clinical trials that reported BP and/or HR as well as the time following administration of topical phenylephrine at which measurements were obtained by concentration of phenylephrine as a mean change and its standard deviation were extracted. Data were synthesized by concentration of phenylephrine and time of measurement following topical application using random-effects models with inverse variance weighting to account for heterogeneity across studies.

MAIN OUTCOMES AND MEASURES Difference in BP and HR after topical administration of phenylephrine.

RESULTS Eight RCTs with a total of 916 participants were included. Data were available for phenylephrine, 2.5%, at 20 to 30 minutes and 60 minutes or longer after administration, and neither BP nor HR changed at either time. Following application of phenylephrine, 10%, BP increased at 5 and 10 minutes (mean difference for both, +15 mm Hg; 95% CI, 11.94-18.54; $P < .001$) but decreased at 20 to 30 minutes and 60 minutes or longer with no changes detected against baseline. A mean increase in HR by 4.48 beats/min (95% CI, 1.09-7.88; $P = .01$) was present at 20 to 30 minutes following application of phenylephrine, 10%, and HR decreased by 60 minutes or longer with no changes detected compared with baseline.

CONCLUSIONS AND RELEVANCE Phenylephrine, 2.5%, leads to no clinically relevant change in BP or HR, and the changes in BP and HR seen with phenylephrine, 10%, are short lived. Thus, phenylephrine, 2.5%, is safe to use in clinical routine.

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Most clinical ophthalmic examinations as well as lens, retinal, and disc imaging involve the administration of topical mydriatic eyedrops to allow for optimal visibility. To achieve good and rapid dilation, phenylephrine hydrochloride (an α -receptor agonist) and tropicamide (muscarinic receptor antagonist) are often combined. Phenylephrine can cause pronounced cardiovascular adverse effects, including increases in both systolic and diastolic blood pressure (BP) and change in heart rate (HR), when given systemically.^{1,2} In contrast, topical tropicamide is thought to be safe and not cause any cardiovascular adverse effects in adults.³

To date, there is no conclusive evidence regarding the cardiovascular adverse effects of phenylephrine, 2.5% or 10%, eyedrops alone or in combination with tropicamide. The largest randomized clinical trial (RCT) that compared phenylephrine, 10% (n = 100) against tropicamide, 1% (n = 50) did not find an increase in BP or HR up to 30 minutes after administration in either group.³ In contrast, a number of case series reported an increase in both BP and HR following topical administration of phenylephrine, 2.5% and 10%, eyedrops.^{2,4} As mounting evidence has indicated that not only both short- and long-term increases in BP but also short-term BP variation in, for example, 24-hour ambulatory BP measurement are associated with the development, progression, and severity of cardiovascular events, target organ damage, and mortality,⁵ it is important to assess the potential adverse effects of topically administered phenylephrine on BP and HR. For example, carotid intima media thickness as well as left ventricular mass index, both measures of target organ damage related to arterial hypertension, could be shown to be significantly elevated in persons with increased systolic 24-hour BP variation.⁶ Thus, it is important to know whether topical phenylephrine leads to any increase in systolic BP, even if it is short lived. In ophthalmic or optometric practice, neither BP nor HR is routinely monitored

before administration of topical phenylephrine, which further increases the necessity for it to be safe.

Against this background, we conducted a systematic review and meta-analysis of the literature to synthesize available evidence on the extent of cardiovascular adverse effects of topical phenylephrine in an effort to determine its safety.

Methods

PubMed, MEDLINE, and the Cochrane Database of Systematic Reviews and Clinical Trials were searched from January 1, 1970, to January 1, 2014, using a combination of the following search terms: *topical, ocular, ophthalmic, phenylephrine, tropicamide, cardiovascular effect, side effect, blood pressure, heart rate, mydriatic, and eye drops*. The searches yielded 2498 articles of which the abstracts were screened. Full texts were obtained for abstracts related to the topic of interest, and their reference lists were cross-checked for additional publications. A total of 70 articles related to the topic were identified and all full texts were retrieved (Figure 1).

Article Selection and Outcomes

Only articles reporting results for adults were included in this review, and all studies reporting results for neonates or infants were excluded. Obtained studies were categorized by study type (retrospective or prospective case series or RCT) and by assessed outcomes (BP, HR, or other). Data from RCTs that reported BP and/or HR as well as the time following administration of topical phenylephrine at which measurements were obtained by concentration of phenylephrine were extracted. Articles that did not report standard deviations and those that did not specify the time of measurement or the concentration of phenylephrine used were excluded (Figure 1). Only data on systolic BP were used for this meta-analysis because systolic BP was consistently reported across studies, with a number of studies not reporting diastolic BP, and has been shown to be a better marker of cardiovascular risk than diastolic BP.⁷ Publication bias in studies was assessed using funnel plots, and selection, ascertainment, and attrition biases were assessed based on study design.

Statistical Analysis

Meta-analysis was performed using Stata version 12.1 statistical software (StataCorp LP), entering HR and BP before topical application of phenylephrine and HR and BP at different times after application as continuous data. The main outcome was mean difference in BP and HR at 20 to 30 minutes and at 60 minutes after topical administration of phenylephrine. Random-effects models with inverse variance weighting were used to account for high degrees of heterogeneity across studies as calculated by I^2 , indicating the percentage of variance in a meta-analysis that is attributable to study heterogeneity.⁸

Results

A total of 8 RCTs that provided data for both phenylephrine, 2.5%, and phenylephrine, 10%, at both 20 to 30 minutes and

Figure 1. Flow Diagram of the Systematic Literature Search

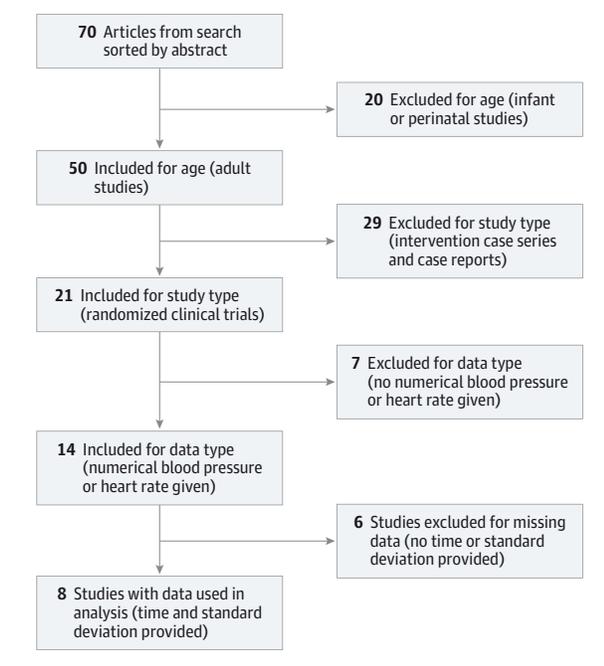


Table. Characteristics of Included Studies

Source	Participants, No.	Age, y	Recruitment Method	Medications Given	Experimental Setup
Bhatia et al, ⁹ 2009	89 (Normotensive, 31 male and 24 female; hypertensive, 10 male and 24 female)	Mean, 50.59 for normotensive and 55.66 for hypertensive	Patients undergoing mydriasis in Oman Sultanate hospital	Phenylephrine hydrochloride, 10%	1 Drop of phenylephrine hydrochloride, 10%, instilled twice, 10-min interval between
Chawdhary et al, ¹⁰ 1984	40	Range, 20-40 y; mean not given	Healthy patients	Phenylephrine hydrochloride, 10%, 5%, 2.5%, and 1.25%	4 Groups of 10 patients; drugs were coded and application was randomized; 1 drop was applied once per 1 min, 3 times in total
Kumar et al, ¹¹ 1985	24 (11 for 10% viscous solution, 13 for 2.5% aqueous solution)	Mean, 42.6 (range, 26-60) for 10% viscous solution; mean, 46.8 (range, 23-81) for 2.5% aqueous solution	Patients undergoing vitreoretinal surgery	All had 1 drop each of cyclopentolate hydrochloride, 1%, and scopolamine hydrobromide, 0.25%, topically; topical viscous phenylephrine hydrochloride, 10%, vs aqueous phenylephrine, 2.5%	Phenylephrine hydrochloride eyedrops were applied during surgery to 1 eye; other eyedrops were applied before surgery, twice
Morgado et al, ¹² 2010	30 (20 female)	Mean, 77.3	Patients undergoing senile cataract surgery	Tropicamide, 1%, and phenylephrine hydrochloride, 10%, eyedrops	1 Drop of each solution, applied 3 times with 5-min intervals, initiated 60 min before surgery
Mouly et al, ¹³ 2006	18 (12 female)	Mean (SD), 26 (5)	Healthy volunteers	Phenylephrine hydrochloride, 10%, plus tropicamide, 0.5%	Mydriatic insert vs 6 drops of topical solution
Symons et al, ¹⁴ 1997	126 (76 female)	Mean, 73.1	Patients undergoing cataract surgery	Phenylephrine, 10%, plus cyclopentolate hydrochloride, 1%	3 Drops administered to eye
Torrón et al, ¹⁵ 2013	35 (20 female)	Mean, 75.53	Patients undergoing cataract surgery	Tropicamide, 1%, phenylephrine hydrochloride, 10%, and cyclopentolate hydrochloride, 1%	1 Drop of each solution instilled at 15-min intervals for 1 h preoperatively
Yospaiboon et al, ¹⁶ 2004	564 (316 female)	Mean (SD), 51.1 (16.79); range, 56-87	Patients at general eye clinic	Tropicamide and phenylephrine hydrochloride, 2.5% or 10%	1 Drop of tropicamide; 30 min later, 1 drop of phenylephrine hydrochloride

60 minutes or longer were included in the meta-analysis (eTable in the Supplement). Three studies tested phenylephrine in combination with tropicamide. All studies are described in detail in the Table. For the 8 RCTs, a total of 916 participants were included; the mean age was 56 years (range, 20-87 years), the sex proportions were approximately equal (54% female), and 3% had known cardiovascular comorbidities such as hypertension. Almost all studies recruited participants at routine eye clinics, either patients prior to ocular surgery or volunteers who most often were patients' escorts. All studies excluded persons with a known history of cerebrovascular or cardiovascular events. Using funnel plots, no evidence of any publication bias was detected (eFigure 1 and eFigure 2 in the Supplement). Selection bias and ascertainment bias have been addressed in most of the included studies by either

randomization or masking (4 of 8 and 5 of 8, respectively), and attrition bias is very unlikely owing to the very short follow-up with all measurements taken within 1 to 3 hours. Thus, all studies were included in the analysis.

Effect on BP

Studies were divided by concentration (2.5% vs 10%), and results were split by time of measurement following topical application (Figure 2 and Figure 3). Phenylephrine, 2.5%, did not cause an increase in BP at either 20 to 30 minutes or 60 minutes or longer after application; in fact, there was a slight decrease in BP at the second time (mean difference, -4.65 mm Hg; 95% CI, -8.54 to -0.76; $P = .02$) (Figure 2).

As the effect of phenylephrine, 10%, may vary over time following application, data were analyzed across all different

Figure 2. Forest Plot of Blood Pressure Changes at 20 to 30 Minutes and at 60 Minutes or Longer After Topical Ocular Application of Phenylephrine Hydrochloride, 2.5%

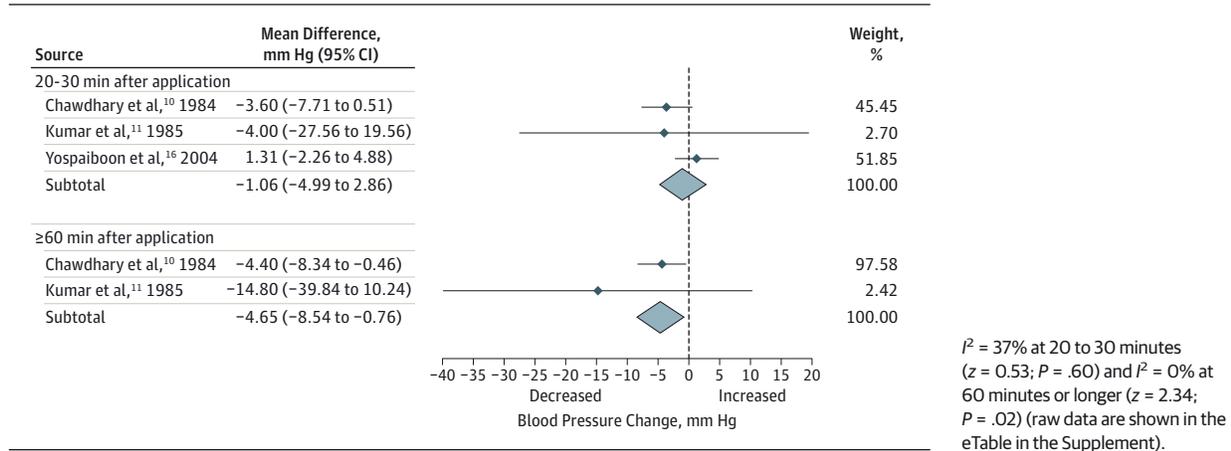
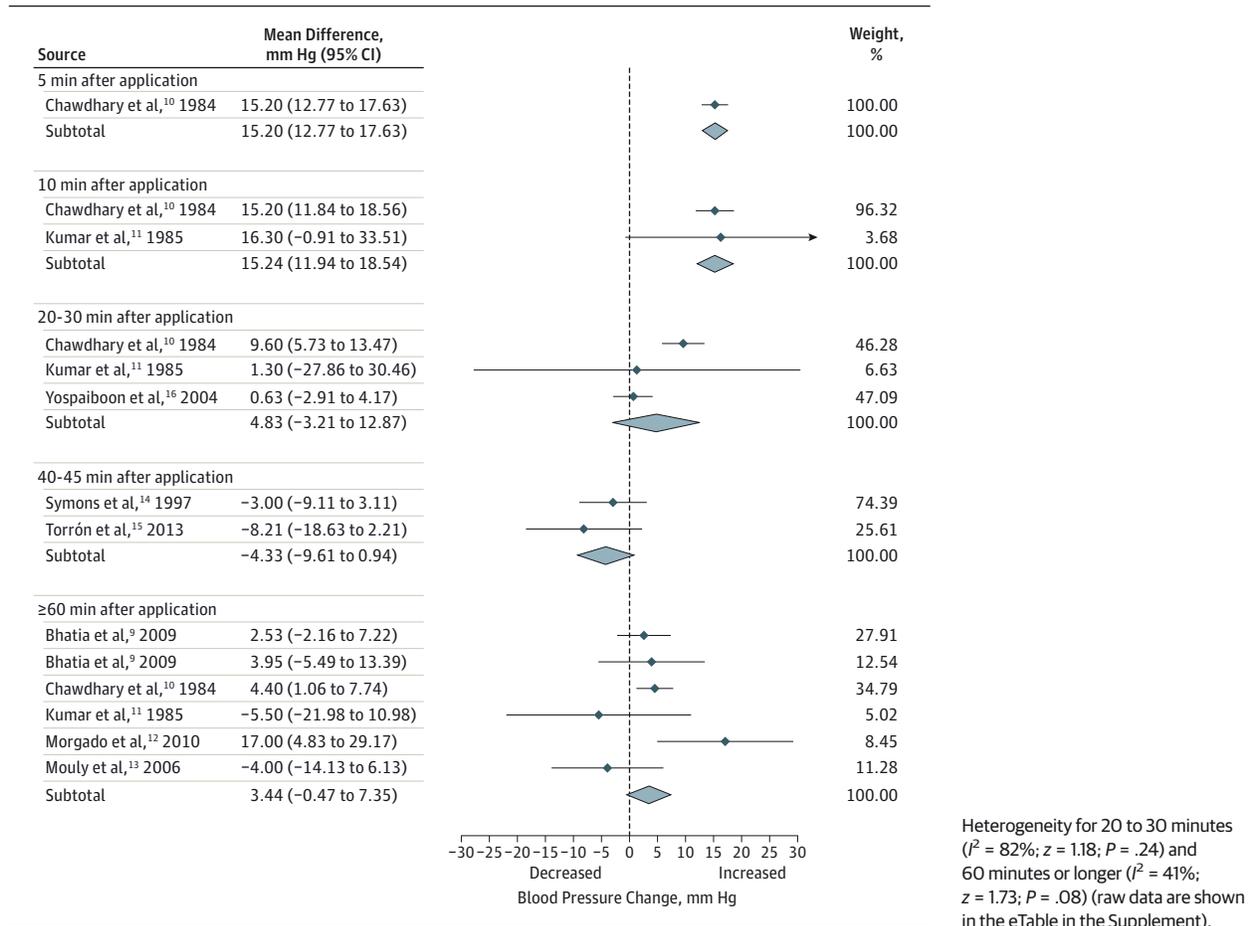


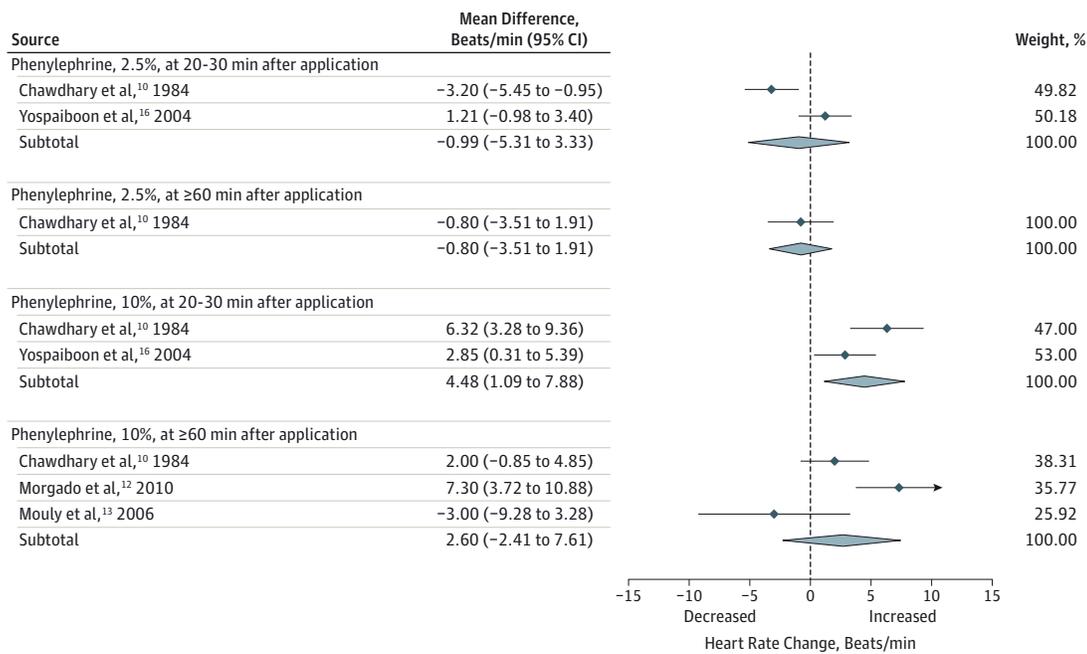
Figure 3. Forest Plot of Blood Pressure Changes at 5, 10, 20 to 30, 40 to 45, and 60 or More Minutes After Topical Ocular Application of Phenylephrine Hydrochloride, 10%



times for which information was available (Figure 3). Topical ocular application of phenylephrine, 10%, led to an increase in BP at 5 and 10 minutes after application (mean difference, +15 mm Hg from a weighted baseline BP of 130 mm Hg; 95% CI, 127-133; $P < .001$), which decreased again to baseline BP at 20 to 30 minutes and remained at this level at 40 to 45 min-

utes and at 60 minutes and longer (changes between -4.3 and +4.8 mm Hg; all $P > .08$) (Figure 3). For both concentrations and times, no studies except that by Kumar et al¹¹ reported any extreme outliers. In the study by Kumar et al, a viscous solution of phenylephrine, 10%, was used, which likely led to greater systemic absorption (Table). As this study provided only

Figure 4. Forest Plot of Changes in Heart Rate After Topical Ocular Application of Phenylephrine Hydrochloride, 2.5% and 10%, at 20 to 30 Minutes and at 60 Minutes or Longer



No heterogeneity detected (raw data are shown in the eTable in the Supplement).

10 cases for each of the concentrations and times (overall weighting <5%) and as viscous phenylephrine is not commonly used in clinical practice, the study's results are not representative of BP and HR changes following phenylephrine application in clinical routine and are only retained as a worst-case scenario. No differences were found between studies that used phenylephrine alone and those that combined it with tropicamide, suggesting that concurrent application of tropicamide has no additional effect on BP.

Effect on HR

Fewer data were available for changes in HR at either time. No change was seen with phenylephrine, 2.5%, at 20 to 30 minutes or at 60 minutes or longer after topical application (Figure 4). At 20 to 30 minutes, mean HR was elevated by 4.48 beats/min (from a weighted baseline of 80 beats/min; 95% CI, 73-87; $P = .01$) following application of phenylephrine, 10%, and it decreased at 60 minutes or longer and was no different from baseline (mean difference, +2.6 beats/min; $P = .31$) (Figure 4). No differences were found between studies that used phenylephrine alone and those that combined it with tropicamide, suggesting that concurrent application of tropicamide has no additional effect on HR.

Discussion

Collating all high-quality data available on the cardiovascular adverse effects of topical ocular phenylephrine, we found no effect of phenylephrine, 2.5%, on BP or HR and only a very short-lived effect of phenylephrine, 10%, which was present

at 5 and 10 minutes after application for BP and up to 20 to 30 minutes for HR. This confirms that phenylephrine, 2.5%, is a safe drug if applied topically. Available data for phenylephrine, 2.5%, are heterogeneous; however, any effect is likely to not be clinically meaningful. As phenylephrine, 2.5%, is very effective in dilating most irises, there is little need to revert to phenylephrine, 10%, in clinical routine.

Previous studies have reported conflicting results, with the only RCT specifically set up to investigate the effect of phenylephrine, 10%, on HR and BP reporting no effect.³ Based on our results, the hazardous effect of phenylephrine, 10%, reported in the literature may have been overstated. The mean change in BP is transient and reverted fully in a short interval of less than 20 minutes. This change also is within a normal physiological range such as changes experienced with circadian or postural BP changes.⁵⁻¹⁷ Almost all systolic BP changes observed were of a magnitude less than 5 mm Hg. A mean systolic BP variation of 12 to 17 mm Hg while awake during the day has been shown to be associated with increased carotid intima media thickness and left ventricular mass index compared with a mean BP variation of 9 mm Hg or less.⁶ In a sample of persons with hypertension with a baseline BP variability of 10 mm Hg per half hour, BP variability at baseline was shown to be associated with target organ damage assessed by presence of arrhythmia, left ventricular mass index, cardiac volume on chest radiography, and retinal hypertensive changes 7 years later, independent of the existing hypertension.¹⁸ In another study, systolic BP variability of 15 mm Hg or less was defined as normal, and an increase more than this was associated with an increased prevalence of ischemic heart disease, severe carotid artery stenosis, and carotid intima media

thickness increases.¹⁹ Thus, a very short-term BP change of less than 5 mm Hg is not likely to be of any clinical relevance.

Similarly, the observed change in HR following topical application of phenylephrine is likely not clinically relevant. The HR increases by 15 beats/min in untrained, healthy individuals 1 minute after standing from a sitting position.²⁰ The changes in HR following topical application of phenylephrine were all less than 10 beats/min for either concentration.

Studies that reported BP and HR changes following application of a combination of topical phenylephrine and tropicamide did not differ from those that applied topical phenylephrine only, which is in keeping with a previously reported lack of effect of topical tropicamide on BP or HR in adults.²

Strengths of this review include the systematic search of literature and meta-analysis. Limitations are the dearth of high-quality evidence, particularly regarding cardiovascular adverse effects of phenylephrine, 2.5%, eyedrops, and the broad range of study designs, small sample sizes, heterogeneous samples, and concurrent application of tropicamide in some

studies. Almost no data are available on cardiovascular adverse effects of topical phenylephrine in persons with cardiovascular risk factors or a history of cardiovascular or cerebrovascular events. The considerable differences between studies are reflected in the high heterogeneity coefficient in our analyses, and we chose to address this by using a random-effects model rather than the more common fixed-effects model. Our overall conclusions are limited by the suboptimal quality of available evidence. Until better evidence becomes available, however, this review constitutes the best evidence available to date.

Conclusions

Phenylephrine, 2.5%, leads to no clinically meaningful change in BP or HR and can be considered safe to use in clinical routine. The changes in BP and HR seen with phenylephrine, 10%, are short lived and of uncertain clinical relevance.

ARTICLE INFORMATION

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Study concept and design: Finger.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Stavert, McGuinness, Finger.

Critical revision of the manuscript for important intellectual content: Harper, Guymer, Finger.

Statistical analysis: Stavert, McGuinness, Finger.

Administrative, technical, or material support: Stavert.

Study supervision: Harper, Guymer, Finger.

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REFERENCES

- Motta MM, Coblenz J, Fernandes BF, Burnier MN Jr. Mydriatic and cardiovascular effects of phenylephrine 2.5% versus phenylephrine 10%, both associated with tropicamide 1%. *Ophthalmic Res.* 2009;42(2):87-89.
- Fraunfelder FW, Fraunfelder FT, Jensvold B. Adverse systemic effects from pledgets of topical ocular phenylephrine 10%. *Am J Ophthalmol.* 2002;134(4):624-625.
- Brown MM, Brown GC, Spaeth GL. Lack of side effects from topically administered 10% phenylephrine eyedrops: a controlled study. *Arch Ophthalmol.* 1980;98(3):487-489.
- Hakim OJ, Orton RB, Cadera W. Topical 2.5% and 5% phenylephrine: comparison of effects on heart rate and blood pressure. *Can J Ophthalmol.* 1990;25(7):336-339.
- Parati G, Ochoa JE, Lombardi C, Salvi P, Bilo G. Assessment and interpretation of blood pressure variability in a clinical setting. *Blood Press.* 2013;22(6):345-354.
- Tatasciore A, Renda G, Zimarino M, et al. Awake systolic blood pressure variability correlates with target-organ damage in hypertensive subjects. *Hypertension.* 2007;50(2):325-332.
- Kannel WB. Elevated systolic blood pressure as a cardiovascular risk factor. *Am J Cardiol.* 2000;85(2):251-255.
- Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327(7414):557-560.
- Bhatia J, Varghese M, Bhatia A. Effect of 10% phenylephrine eye drops on systemic blood pressure in normotensive and hypertensive patient. *Oman Med J.* 2009;24(1):30-32.
- Chawdhary S, Angra SK, Zutshi R, Sachdev MS. Mydriasis: use of phenylephrine (a dose-response concept). *Indian J Ophthalmol.* 1984;32(4):213-216.
- Kumar V, Schoenwald RD, Chien DS, Packer AJ, Choi WW. Systemic absorption and cardiovascular effects of phenylephrine eyedrops. *Am J Ophthalmol.* 1985;99(2):180-184.
- Morgado G, Barros P, Martins J, Lima A, Martins N. Comparative study of mydriasis in cataract surgery: topical versus Mydrasert versus intracameral mydriasis in cataract surgery. *Eur J Ophthalmol.* 2010;20(6):989-993.
- Mouly S, Mahé I, Haoouchine B, et al. Pharmacodynamics of a new ophthalmic mydriatic insert in healthy volunteers: potential alternative as drug delivery system prior to cataract surgery. *Basic Clin Pharmacol Toxicol.* 2006;98(6):547-554.
- Symons RC, Walland MJ, Kaufman DV. A comparative study of the efficacy of 2.5% phenylephrine and 10% phenylephrine in pre-operative mydriasis for routine cataract surgery. *Eye (Lond).* 1997;11(pt 6):946-948.
- Torrón C, Calvo P, Ruiz-Moreno O, Leciñena J, Pérez-Iñigo A. Use of a new ocular insert versus conventional mydriasis in cataract surgery. *Biomed Res Int.* 2013;2013:849349.
- Yospaiboon Y, Luanratanakorn P, Noppavinyoowong C. Randomized double-blind study of phenylephrine 2.5% vs 10% on pupillary dilation. *J Med Assoc Thai.* 2004;87(11):1380-1384.
- Chugh AR, Loughran JH, Slaughter MS. Circadian variations in blood pressure in health and disease: implications for patient management. *Chronophysiol Ther.* 2011;1:17-31. doi:10.2147/CPT.S15597.
- Manios E, Stamatelopoulos K, Tsivgoulis G, et al. Time rate of blood pressure variation: a new factor associated with coronary atherosclerosis. *J Hypertens.* 2011;29(6):1109-1114.
- Sander D, Kukla C, Klingelhöfer J, Winbeck K, Conrad B. Relationship between circadian blood pressure patterns and progression of early carotid atherosclerosis: a 3-year follow-up study. *Circulation.* 2000;102(13):1536-1541.
- Borst C, Wieling W, van Brederode JF, Hond A, de Rijk LG, Dunning AJ. Mechanisms of initial heart rate response to postural change. *Am J Physiol.* 1982;243(5):H676-H681.