Original article

Hemodynamic effects of intraocular epinephrine during cataract surgery: a double blinded placebo controlled randomized clinical trial

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Abstract

Objective: To evaluate hemodynamic effects of intraocular epinephrine irrigation in patients undergoing cataract surgery.

Materials and methods: This study was conducted as a prospective double blinded clinical trial at the Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

Eighty-eight patients of age 38-90 years undergoing were randomly allocated into two groups: Group E received intraocular irrigation fluid (balanced salt solution) with epinephrine 1:1000, 000, and group C received intraocular irrigation fluid (balanced salt solution) without epinephrine. Heart rate (HR), systolic and diastolic blood pressure (SBP, DBP) were measured before and at 5, 10, 15 minutes after starting intraocular infusion of epinephrine1:1000, 000 in both groups.

Results: HR and SBP were similar in the two groups at different time intervals. DBP was decreased at 5 minutes after epinephrine administration in the epinephrine group and increased at 10 and 15 minutes but there was no significant differences between the two groups.

Conclusion: Intraocular infusion of epinephrine 1:1,000,000 can be used during cataract surgery without hemodynamic side effects and so is a safe and effective method for this purpose.

Key-words: hemodynamic, intraocular, epinephrine

Introduction

Cataract surgery is the most commonly performed intraocular procedure (McCormic etal 2006). It requires a satisfactory degree of mydriasis throughout the entire operation (Mouly et al 2006). Failure to maintain mydriasis during surgery can increase the risk of damage to the iris, incomplete clearance of soft lens matter or more importantly, rupture of the posterior capsule (Corbett et al 1994). For this purpose, many studies suggest different drugs, such as phenylephrine, tropicamide, and epinephrine (Duffin et al 1982; Liou et al 1998; Schlichtenbrede et al 2001). On the other hand, eye surgery patients are a high-risk group. Because of increased age in adult patients, they are likely to have other risk factors, such as diabetes, hypertension, and

Received on: 13.11.2011 Accepted on: 22.03.2012
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atherosclerosis (Kubitz et al, 2003). In a study by Hu et al (2001), cataracts have been indicated as a marker for increased mortality.

Epinephrine (also known as adrenaline) is a hormone and a neurotransmitter (Berecek, 1982). Adverse reactions to adrenaline include palpitations, tachycardia, arrhythmia, anxiety, headache, tremor, hypertension, and acute pulmonary edema (Elliot et al, 1989). Because of the potential hemodynamic adverse effects of epinephrine (Elliot et al, 1989; Gimbel, 1989), those effects in patients undergoing cataract surgery with intraocular epinephrine irrigation were assessed in this prospective clinical trial study.

Materials and methods

Study duration and location

After approval from the university institutional ethics committee, this double blinded placebo controlled randomized clinical trial was carried out between October 2007 and April 2008 in the Shahid Sadoughi General Hospital, Yazd, Iran.

Study population and method

Eighty-eight patients (32 men and 56 women) aged between the ages of 38-90 years undergoing routine extra capsular cataract extractions were randomly allocated into two groups by simple sampling. Patients were chosen for each group (with consideration of following parameters: $p<0.05$ as significance, test power of 80%, d=1.5 and based on previous studies S=2). Written consent was obtained from all patients. All patients were in ASA class I and II, without any airway, the systemic and psychological problems. Patients did not use any drugs during 24 hours prior to the procedure. All patients had no history of sensitivity to anaesthesia or the study drug. Group E received intraocular irrigation fluid (balanced salt solution) with epinephrine 1:1,000, 000, and Group P (Placebo) received intraocular irrigation fluid (balanced salt solution) without epinephrine. All operations were performed by the same surgeon with the same technique. The patients gave informed consent before inclusion in the trial. Exclusion criteria included patients with an allergy to any of the drugs used and those undergoing any therapy interfering with hemodynamic parameters. The patients received fentanyl (1µg/kg) as premedication. Induction and maintenance of anesthesia were the same for all the patients using a laryngeal mask airway and controlled ventilation. The patients received propofol(1.5 mg/kg) and atracurium (0.4 mg/kg) at induction of anesthesia, and maintenance of anesthesia was with isoflurane 0.5 MAC. Ventilation was controlled with laryngeal mask ventilation. At the end of the surgery, muscle relaxant was reversed by intravenous atropine and prostigmine.

Age, sex, history of any disease, especially diabetes, hypertension, ischemic heart disease, and any medication use in the patients were noted. Hemodynamic parameters (heart rate, systolic and diastolic blood pressure) were measured by the anesthesia resident (who was blind to the study groups) before (baseline) and 5, 10, 15 minutes time intervals after starting intraocular infusion of epinephrine1:1,000, 000. Any form of arrhythmia was registered during this period. The study flow is described in figure 1.

Study analysis

The Student's t-test was used for analysis of the patient's age .The X^2 test was used for the sex of the patients and history of diabetes, hypertension, and Fisher's exact test was used for history of IHD in the patients. The paired –t-test was used in statistical analyses of heart rates, systolic and diastolic blood pressure of the patients 5, 10, and 15 minutes after infusion comparing with the baseline in each group and one way ANOVA was used for comparing HR ,DBP, and SBP in different times in two groups.

The data were analyzed with Statistical Package for the Social Sciences (SPSS) Version 16 for Windows (SPSS Inc.USA). P values less than 0.05 were considered significant.

Results

Demographic data of study population is given in table 1. There were no significant differences between the two groups with regards to sex, age, history of diabetes, hypertension and IHD.

Also, there was no significant difference between the two groups with regard to baseline HR, SBP and DBP (P>0.05) before starting infusion of epinephrine (Table 2). Overtime, HR increased in each group when compared with baseline rates, but this change was not significant (P>0.05). The data showed that there were significant differences between two groups according to HR (P>0.05, Table2). There was a statistically significant decrease in SBP after 5 and 10 minutes and a slight increase after 15 minutes when compared with baseline pressures in each group, but there were no significant differences between two groups at any measure times (p>0.05) (Table 2).

In Group E (Epinephrine), DBP was decreased significantly at 5th minute (P<0.05), but the differences between values were not significant after 10 and 15 minutes compared with data on baselines (p>0.05). In Group P there was no significant change comparing with baseline pressure at any study times (p>0.05). Also, there were no significant differences between the two groups at any time measured in the study (p>0.05, Table 2).

Table 1

Comparison of demographic data between the groups

	Group Epinephrine (n=45)	Group Placebo (n=43)	P value
Age (years)	68.32 + 9.9	67+ 11.7	0.573
Sex (male/ Female)	16/29	16/27	0.872
Diabetes	9(20%)	10(23.26%)	0.711
Hypertension	4(8.9%)	9(20.93%)	0.112
IHD	2(4.44%)	7(16.28%)	0.086

Age is shown as mean ± standard deviation. Diabetes, Hypertension and IHD are shown as frequency (%). There were no significant differences in baseline characteristics between two groups.

Table 2

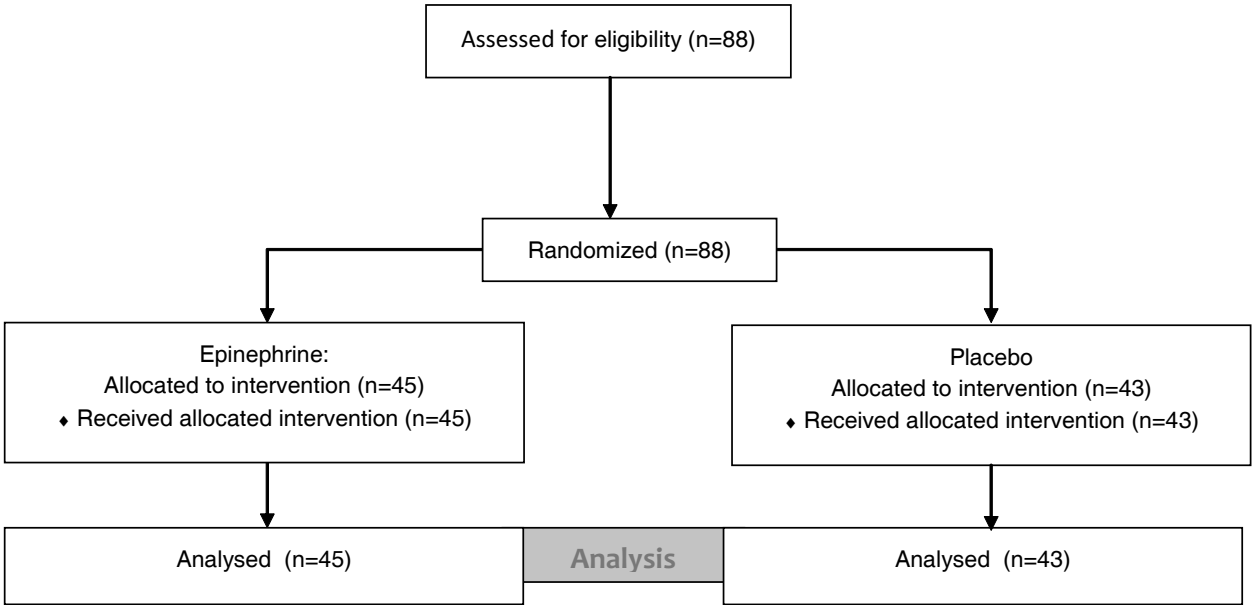
Hemodynamic parameters in two groups at different time

HR (beat/minute)	Baseline	T5	T10	T15
Epinephrine	77.60±13.1	87.95±13.59	85.40±12.79	84.79±13.37
Placebo	80.22±15	88.36±12.99	87.64±13.24	86.51±13.69
P value	0.386	0.887	0.420	0.553
SBP (mmHg)				
Epinephrine	136.6 ±22.3	110.76±24.71	118.35±26.92	120.49±28.69
Placebo	142.6 ±21.1	124.44±24.98	123.91±22.97	124.96±23.81
P value	0.196	0.835	0.12	0.048
DBP (mmHg)				
Epinephrine	81.70±12.1	70.79±14.33	74.79±16.57	74.86±17.87
Placebo	81.2±8.8	77.18±15.35	77.64±14.13	78.24±13.98
P value	0.299	0.386	0.428	0.324

HR, SBP and DBP are shown as mean ± standard deviation. There were no significant differences in hemodynamic characteristics between two groups. Maximum of variation is shown in SBP (18.92%) between baseline and T5 and this variation for HR and DBP are about 13.35%. With repeated measurement these differences between different times are not significant.

Figure 1

Flow of study: Hemodynamic effects of intraocular epinephrine during cataract surgery



Discussion

Many agents with different concentrations and methods are used to maintain mydriasis during cataract surgery. There are many studies which assess the mydriatic and hemodynamic effects of these agents. Irrigation fluid containing epinephrine is thought to be of benefit in this respect (Liou et al 1998; Lou et al 2001; Schouwenberg et al 2006). Epinephrine is a synthetic sympathomimetic drug. It interacts with alpha, beta 1 and beta 2 adrenergic receptors, the stimulation of which depends on the plasma concentration. At low plasma concentration, epinephrine primarily stimulates beta adrenergic receptors, leading to increased HR (beta 1) and peripheral vasodilatation (beta 2). At higher concentration, alpha adrenergic activity starts to prevail, causing increased vascular tone and blood pressure (Schouwenberg et al 2006). Epinephrine maintains mydriasis by direct action on the dilator papillae of the iris (Corbett et al 1994). Different concentrations of epinephrine are used and there are many studies assess the pupillary responses to these various doses (Corbett et al 1994; Schouwenberg et al 2006; Fell et al 1989). Two studies showed that commercial epinephrine 1:1000 with its preservative sodium bisulfate damaged corneal endothelial function and ultra-structure in rabbit and monkey eyes with sodium bisulfate being the main cause of the damage (Edelhauser et al 1982; Hull et al 1976). They concluded that endothelial damage can be prevented by dilution of epinephrine. Duffin et al studied the pupillary responses to various doses of intraocular epinephrine (Duffin et al, 1983). They concluded that epinephrine concentrations of 1:96,000 or less may be effective in maintaining mydriasis during cataract surgery. Corbett et al demonstrated that epinephrine 1:1,000, 000 in the intraocular infusion is of significant benefit in maintaining mydriasis during cataract surgery (Corbett et al 1994). One advantage of giving epinephrine in the irrigation fluid, as opposed to a bolus, is that it continues to enter the eye while the stimulus to miosis persists, because during surgery there is a tendency for the pupil to constrict, particularly following manipulation of the iris. As epinephrine is administered over a longer time period by infusion than by injection, a more

dilute concentration can be used (Corbett et al 1994). Because of the previous studies that demonstrated epinephrine 1:1,000, 000 is effective for maintaining mydriasis during cataract surgery, we used the same concentration of intraocular infusion of epinephrine 1:1,000, 000 in our study (Corbett et al 1994; Liou et al 1998).

Systemic absorption of epinephrine infused into the eye can potentially occur via the vascular structures of the anterior segment and via the nasolacrimal duct from overspill into the conjunctional sac (Liou et al 1998). Because of potentially adverse cardiovascular side effects of absorbed epinephrine during intraocular infusion, the hemodynamic effects of intraocular infusion of epinephrine 1:1,000,000 in this study was assessed.

In another study of intraocular irrigation with 1:500,000 epinephrine, plasma concentration of epinephrine and noradrenalin did not differ significantly from those noted before induction of anesthesia (Fell et al 1989). In a similar study on a mixed population of patients receiving local or general anesthesia, there was no significant changes in blood pressure or heart rate during the time of epinephrine administration (Fiore et al 1988). In addition, Yamaguchi et al concluded that both patients with or without hypertension incurred no additional risk of significant changes of either arterial blood pressure or heart rate during intraocular epinephrine irrigation at a concentration which maintain pupil dilation (Yamaguchi et al 1988). In Liou SW et al study, pulse rate and blood pressure in patients of the study group, even those with hypertension, showed no significant fluctuation during the surgery (Liou et al 1998). Later, Liou SW et al found that blood pressure did not elevate after injection of epinephrine 1:400,000 (Liou et al 2001). In our study, the patients in the study group, even those with hypertension, showed no increase in blood pressure or in heart rate. In the present study, after 5 minutes following intraocular infusion with epinephrine (1:1000, 000), DBP decreased significantly, but these values were restored 5 minutes later. There were no significant differences in these parameters after 10 and 15 minutes in both groups. These findings are comparable to a study by Yang et al (2005). In their study, blood pressure was significantly affected after infiltration with epinephrine 1:200,000 in functional endoscopic sinus surgery (FESS) with decreasing SBP, DBP and MAP at 1 and 1.5 minutes after infiltration. Various studies have shown that changes in vital parameters after infiltration of epinephrine depend on the physical status of the patient, the amount of vasopressor used, the vascularity of the site of administration and its rate of absorption. Because the nasal area is a highly vascular area and absorption of epinephrine is rapid, lower BP was observed 1 minute after infiltration and was restored quickly 1 minute later. Homma and associates also found that the mean plasma epinephrine concentration reached a maximum 3 minutes after infiltration of epinephrine during dental treatment. In this study, 5 minutes after intraocular infusion of epinephrine (1:1000,000), DBP decreased significantly but was restored at 5 minutes (Homma et al 1999). There was no significant difference in DBP between the two groups after 10 and 15 minutes. This may be related to the slower absorption of epinephrine from the eye. Systemic absorption of epinephrine infused into the eye can potentially occur via the vascular structures of the anterior segment and via the nasolacrimal duct from spillover into the conjunctival sac (Liou 1998). In Yang's study, a slight increase in HR was recorded with hypotension. In the present study, a decrease in DBP was not associated with tachycardia, which may be because of concurrent fentanyl use at the time of anesthesia induction. In another animal study (Schlag et al, 2012), the hemodynamic effects of sub-mucosal injection of two volumes of adrenaline (1:10,000) into different parts of the upper gastrointestinal track during endoscopy in pigs were assessed. The results of this study showed significant hemodynamic changes after endoscopic sub-mucosal injection of adrenaline especially in the esophagus. The difference between the results of

this study with ours is due to the differences in site of injection, and the concentration of adrenaline. In our study, we used adrenaline at a concentration of 1:1,000,000 and the vascularity of esophagus is much more than intraocular, therefore our results did not show any significant hemodynamic changes. This suggests that the effect of injection site epinephrine concentration can exert an effect on the hemodynamic situation.

Conclusion

Intraocular infusion of epinephrine 1:1,000,000 is a safe and effective method to maintain mydriasis during cataract surgery without adverse cardiovascular side effects.

Acknowledgments

The authors thank Mohammad Reza Samiei MD, Department of Anesthesiology, School of Medicine, Shahid Sadoughi University of Medical Sciences And Health Services, Yazd, Iran.

Source of support: This study was conducted under financial support of Faculty of Medicine, Shahid Sadoughi University of Medical Sciences.

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Source of support: acknowledged. Conflict of interest: none