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Original Research Article

Comparative Study between Preloading with Fluids Vs Phenylephrine in the Management of the Hypotensive Effects of Propofol in Patients Undergoing Rapid Sequence Intubation

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Abstract

Introduction: The induction of general anaesthesia with propofol has been associated with a decrease in systolic arterial blood pressure. Various strategies have been attempted to prevent this hypotension with inconclusive evidence. Ketamine, ephedrine, atropine, glycopyrolate, dopamine, dobutamine etc have been administered in various studies to prevent this hypotension with various results.

Aims and Objective: Present study was undertaken to compare, the effect of preloading with crystalloid (Ringer lactate) and the effect of prophylactic administration of intravenous phenylephrine against the hypotensive effects of induction of anesthesia with propofol in rapid sequence intubation.

Material and Methods: After taking ethical committee clearance and written informed consent from every patients randomly selected 60 patients aged between 18-50 years, ASA grade I-II, Mallampati class I-II posted for elective surgical procedure requiring general anaesthesia were included in the a prospective, randomized, single blind study study. Group R-Patients (30) who received Inj Propofol (2.5mg/kg) & 10-15 ml /kg Ringer lactate 10 minutes prior to induction of anaesthesia and Group P –Patient who received inj propofol (2.5mg/kg) & inj phenylephrine 0.1 mg intravenously before induction of anaesthesia. Haemodynamic parameters (HR, SBP, DBP and MAP) were monitored & recorded in following specific time intervals: Before the starting of anaesthesia (baseline value), Just before intubation and 1, 2, 3, 4, 5, 10 minute after intubation.

Results: All the patients of two study groups were comparable with respect to sex, age, height, weight. No significant differences were observed between the groups (p value >0.05). During the

entire process of intubation up to 10 minutes, heart rate was significantly lower in Group P compared to Group R. However the mean heart rate was within the physiological limit. In group P the systolic, diastolic, mean arterial pressure all significantly increased in the first two reading than reading taken just before in the intubation. Then the pressure gradually tends to normalise for upto 10 minutes.

Conclusion: Phenylephrine infusion in the dose of 100 microgram is effective in obtunding hypotension caused by propofol induction with minimal side effects and is a better option than crystalloid infusion.

Keywords : Propofol, Induction, Hypotension, Phenylrphrine, Ringer lactate

Introduction

Intravenous sedatives and hypnotics are probably the most important class of pharmacologic agents which are more central to the practice of anaesthesiology [1]. In 1977, propofol was introduced as a strong anaesthetic drug and now a days is one of the most common drugs used in the induction of anaesthesia. Administration of propofol, 1.5 to 2.5 mg/kg IV as a rapid IV injection (<15 seconds) produces unconsciousness within about 30 seconds. Awakening is more rapid and complete than that after induction of anesthesia with all others drugs used for rapid IV induction of anesthesia [2].

The induction of general anaesthesia with propofol, however, has been associated with a decrease in systolic arterial blood pressure [3]. The hypotensive effects of propofol has been attributed to a decrease in systemic vascular resistance caused by combination of venous and arterial vasodilatation. It has also been postulated that propofol acts as an L-type calcium channel antagonist to decrease peripheral resistance and initiate hypotension. Depression of myocardial contractility and impaired baroreflex mechanism also play a role [2,3].

Various strategies have been attempted to revent this hypotension with inconclusive evidence. Ketamine, ephedrine, atropine, glycopyrolate, dopamine, dobutamine etc have been administered in various studies to prevent this hypotension with various results [4]. Fluid preloading with colloid and crystalloid has also been used to prevent the hypotensive effects of induction of anaesthesia with these drugs. The present study was undertaken to compare, the effect of preloading with crystalloid (Ringer lactate) and the effect of prophylactic administration of intravenous phenylephrine against the hypotensive effects of induction of anesthesia with propofol in rapid sequence intubation.

Material and Methods

The prospective, randomized, single blind study was conducted in general operation theatre of a tertiary medical centre after taking ethical committee clearance and written informed consent from every patients in period of one year. Randomly selected 60 patients aged between 18-50 years, ASA grade I-II, Mallampati class I-II posted for elective surgical procedure requiring general anaesthesia were included in the study.

Patients having history of allergy either to propofol /phenylephrine, systemic illness, pregnancy, patient on beta blocker or digoxin therapy, anticipated difficult airway, difficulty in laryngoscopy & intubation taking time >30 seconds or requiring >2 attempt were excluded from our study.

Patients were allocated by systematic randomization in order to ensure equal number of patients in each group and to avoid bias. The first patient was randomly chosen and allocated to the first group (Group-R) using computer generated random number table. The following patient was automatically allocated to the subsequent group i.e, group R and then again group P. The order was frequently reversed to avoid bias. Group R-Patients who received Inj Propofol (2.5mg/kg) & 10-15 ml /kg Ringer lactate 10 minutes prior to induction of anaesthesia, Group P –Patient who received inj propofol (2.5mg/kg) & inj phenylephrine 0.1 mg intravenously before induction of anaesthesia.

On the day before surgery pre anesthetic check-up were performed. Patients advised to take nil per mouth (NPM) for 8 hours prior to surgery. All patient were given tab diazepam 0.2 mg/kg orally at bedtime on the previous night of surgery . On the day of surgery after confirmation of patient identity and NPM status, patients were shifted to the operating room & multiparameter monitors were attached to the patients. Basal systolic blood pressure, diastolic blood pressure, mean arterial pressure, heart rate, ECG, and oxygen saturation (SpO_2) were recorded. Continuous monitoring of the vital parameters were done.

An intravenous line was secured with an appropriate size cannula. All patients were premedicated with inj Ondansetron (0.1mg/kg), Inj Fentanyl (2µg /kg), Inj Glycopyrolate (10µg/kg), inj Lidocaine 1.5mg/kg intravenously and pre oxygenated for 3 minute by face mask. The induction was done by giving Inj. Propofol (2 mg/kg) and muscle relaxation was done by giving Inj. Succinylcholine 1 mg/kg. Appropriate method of rapid sequence induction was followed. Laryngoscopy and intubation was done by using appropriate sized cuffed endotracheal tube. Maintenance of anaesthesia was done by using N_2O:O_2 at the ratio of 66:33, intermittent dose of Inj. vecuronium, analgesics and intravenous fluids based on requirements. The patients were reversed by giving Inj. Neostigmine (0.04mg/kg) and Inj. Glycopyrolate (0.01mg/kg). Haemodynamic parameters (HR, SBP, DBP and MAP) were monitored & recorded in following specific time intervals: Before the starting of anaesthesia (baseline value), Just before intubation and 1, 2, 3, 4, 5, 10 minute after intubation.

Statistical Analysis

All data were collected & compared and statistically analysed using SPSS STATISTICS VERSION 20, 2012. Qualitative data (sex) were compared between groups with Chi – Square test (x2) and quantitative data (age, height, body weight, heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure etc.) were compared between groups with T test and Mann-Whitney U test. Hemodynamic parameters within groups at different time intervals were compared with base line value with T test. A p value <0.05 was considered statistically significant and <0.01 was considered as highly significant.

Results

All the patients of two study groups were comparable with respect to sex, age, height, weight. No significant differences were observed between the groups (p value >0.05).

Table 1: Comparison of demographic data (age, body weight & Height) among two groups.

Demographic variables	Group R (n=30) (Mean ±SD)	Group P (n=30) (Mean±SD)	p value
Sex (M:F)	(11:19)	(12:18)	0.791
Age (YRS)	32.77±7.44	32.87±6.86	0.994
Body Weight (Kg)	56.23±7.64	58.57±6.05	0.227
Height (Cm)	159.13±9.59	159.47±10.11	1.000

Table 2: Comparison of heart rates between the two study groups at different points of time

Time interval	Group R (n=30) (Mean±SD)	Group P (n=30) (Mean±SD)	P value
Before the starting of anesthesia (Baseline)	82.83±14.444	83.57±11.554	0.636
Just before intubation	81.77±11.252	69.77±11.346	0.000 **
1 minute after intubation	80.60±9.708	63.50±10.792	0.000 **
2 minute after intubation	77.20±8.062	60.17±9.924	0.000 **
3 minute after intubation	75.03±7.122	58.90±8.535	0.000 **
4 minute after intubation	74.20±7.699	59.70±8.082	0.000 **
5 minute after intubation	73.10±7.241	60.47±7.969	0.000 **
10 minute after intubation	72.77±7.877	61.53±8.068	0.000 **

Baseline heart rate in both group were comparable (p value -0.636). After phenylephrine infusion the heart rate was significantly lower in Group P compared to Group R. However this decrease in mean heart rate was within the physiological limits.

During the entire process of intubation up to 10 minutes, heart rate was significantly lower in Group P compared to Group R. However the mean heart rate was within the physiological Limit.

Table 3: Comparison of systolic blood pressure between the two study groups at different points of time

Time interval	Group R (n=30) (Mean±SD)	Group P (n=30) (Mean±SD)	P value
Before the starting of anesthesia (Baseline)	128.77±8.617	127.03±7.458	0.491
Just before intubation	106.37±13.952	162.43±8.553	0.000 **
1 minute after intubation	97.67±8.222	142.23±8.316	0.000 **
2 minute after intubation	100.37±6.584	127.47±7.200	0.000 **
3 minute after intubation	104.57±6.415	119.37±6.457	0.000 **
4 minute after intubation	108.23±5.412	113.83±6.368	0.000 **
5 minute after intubation	109.17±5.434	112.00±5.051	0.000 **
10 minute after intubation	110.67±5.903	111.20±5.020	0.573 **

Table 4: Comparison diastolic blood pressure between the two study groups at different points of time

Time interval	Group R (n=30) (Mean±SD)	Group P (n=30) (Mean±SD)	P value
Before the starting of anesthesia (Baseline)	82.20±6.365	78.73±6.898	0.072
Just before intubation	64.23±9.825	95.10±6.348	0.000 **
1 minute after intubation	61.80±7.703	82.33±5.996	0.000 **
2 minute after intubation	63.10±7.572	78.07±5.681	0.000 **
3 minute after intubation	64.47±6.606	75.17±5.559	0.000 **
4 minute after intubation	65.67±7.531	74.40±5.405	0.000 **
5 minute after intubation	67.53±6.124	74.37±4.927	0.000 **
10 minute after intubation	68.30±6.929	73.23±5.177	0.004**

Table 5: Comparison Mean arterial blood pressure between the two study groups at different points of time

Time interval	Group R (n=30) (Mean±SD)	Group P (n=30) (Mean±SD)	P value
Before the starting of anesthesia (Baseline)	97.73±6.633	94.90±6.266	0.135
Just before intubation	78.20±10.526	117.43±5.482	0.000 **
1 minute after intubation	73.83±6.492	102.27±5.245	0.000 **
2 minute after intubation	75.60±6.196	94.50±5.097	0.000 **
3 minute after intubation	77.80±5.659	89.83±4.647	0.000 **
4 minute after intubation	79.90±6.116	87.57±4.861	0.000 **
5 minute after intubation	81.47±5.111	86.83±3.966	0.000 **
10 minute after intubation	68.30±6.929	73.23±5.177	0.004**

Baseline systolic, diastolic and mean arterial pressure were comparable between the group R and group P. After infusion of propofol the mean blood pressure (systolic, diastolic and mean arterial) were significantly reduced in patients of group R. There was significant reduction of systolic blood pressure which even decreased more than 20% in the first three reading then it returned towards baseline in patients of group R .In case of diastolic blood pressure there is also more than 20 % reduction in the first three readings (upto 2 minute after intubation). Then it gradually returned towards baseline. Findings were similar with mean arterial pressure. But in group P the systolic, diastolic, mean arterial pressure all significantly increased in the first two readings than the reading taken just before in the intubation. Then the pressure gradually tends to normalise for upto 10 minutes.

From the table 2 and table 5 we can see that there is a significant difference between the heart rates and blood pressures between group R and group P. Blood pressure and heart rate in group P are closer to the baseline value of the patients. It is also seen that in group P values just after completion of phenylephrine infusion mean SBP, DBP & MAP are significantly higher than group R with fluid, but it is also seen that the mean value of group P were within 25% of mean baseline value. From the heart rate we can see that just before intubation the heart rate of group P were significantly lower than group R. However, this decrease is within the normal range and this persisted for 10 minutes after intubation.

Discussion

Hypotension secondary to vasodilation occurs due to the vasodilator drugs specially intravenous and volatile anesthetic agents. Tissue hypoxia seldom occurs if adequate precautions are maintained. Failure to maintain adequate blood pressure may cause ischemic brain damage, myocardial ischemia, renal ischemia and ischemic retinal blindness. This prospective, randomized, single blind study was undertaken to compare the usefulness of intravenous fluid (Ringer's lactate) and phenylephrine (3-hydroxyphenylethylamine, a synthetic non-catecholamine which principally stimulates alpha -1 adrenergic receptors by a direct effect) in prevention of hypotension during propofol induction.

The blood pressure effect of propofol may be exaggerated in hypovolemic patients, elderly patients and patients with compromised left ventricular function [5]. Propofol may decrease sympathetic nervous system activity to a greater extent than parasympathetic nervous system activity, resulting in a predominance of parasympathetic activity. Propofol does not alter sinoatrial or atrioventricular node function in normal patients or in patients with Wolff-Parkinson –White syndrome [6]. Marked fluctuation in hemodynamic response have been also reported in geriatric patients. Therefore, patients with an optimal range of 18 to 50 years were selected for this study so that it guides our judgement in compromised patients. Difficult intubation takes longer time and is invariably associated with marked hemodynamic change even in well premedicated patients. So, patients with higher Mallampati class (III and IV) have been excluded from this study [7].

Patients with systemic disease were also excluded as they might exhibit a variable presor response following induction. Direct myocardial depression and reduction in systemic vascular resistance by propofol have been implicated as important factors in producing cardiovascular depression. In addition to arterial vasodilation, propofol produces venodilation due to both to a reduction in sympathetic activity and a direct effect on the vascular smooth muscle, which further contributes to its hypotensive effect [8].

Experiments in isolated myocardium suggest that the negative inotropic effect of propofol results from a decrease in intracellular calcium availability secondary to inhibition of trans- sarcolemmal calcium influx [9]. Propofol alters the baroreflex mechanism. As a result despite decrease in systemic blood pressure, heart rate typically remains unchanged [10]. Study conducted by Clayeys *et al*. suggested that the major haemodynamic effect of propofol is a decrease in arterial pressure as a result of decrease systemic vascular resistance [11] which may be more severe if patient is already on vasodilator therapy such as alpha -1 blocker [12]. Vasoconstriction is indicated during episodes of systemic hypotension, especially in drug-induced vasodilatation as with propofol. Vasoconstrictors are useful adjuncts in the prevention and treatment of ischemia owing to their ability to increase systemic blood pressure. In a study done by Y Dhungana *et al* compared the efficacy of preloading with colloid with vasoconstrictor (intravenous ephedrine sulphate) in preventing hypotension during propofol induction.

They concluded that though preloading with colloids (haemaccel) or prior injection of sympathomimetics (ephedrine) are not fully efficacious in preventing hypotension caused by propofol induction, both decrease the incidence in significant number of patients with heart rate less than baseline valuen [13]. In our study in group P patients has significantly lower heart rate than the patients of group R. In our study phenylephrine was not associated with increase in heart rate. It caused bradycardia with significant reduction of heart rate from baseline value which is not

so significant hemodynamically. The preloading with ringer lactate was also not very effective to completely obtund the response of propofol induced hypotension.

EL-Tahan MR *et al*. administered saline, ephedrine (0.07, 0.1 or 0.15 mg/kg), or phenylephrine 1.5ug/kg before induction of propofol –fentanyl anesthesia and concluded that prophylactic use of small doses of ephedrine (0.07-0.1 mg/kg) is safe and effective in the counteraction of propofol induced hypotension [14]. Those who received phenylephrine showed greater rise in systemic vascular resistance, reduced cardiac index, stroke volume and left ventricular stroke work and more frequent ischemic episodes. In one study Imran M *et al* concluded that phenylephrine in a dose of 100 microgram is more effective than 50 microgram to prevent hypotension with propofol [15]. Turner RJ *et al* in 1998 concluded that administration of a fluid preload did not attenuate the decrease in systolic arterial pressure after induction of anaesthesia with propofol and fentanyl [16].

The observation of our study suggested that preloading with Ringer lactate was insufficient to completely obtund the hypotensive effects; however phenylephrine at 100 microgram dose was very effective to obtund the hypotensive effect of propofol (Hypotension was defined as the 20% reduction in blood pressure than the baseline value).

Phenylephrine in 100 microgram dose sustained systolic blood pressure, diastolic blood pressure and mean arterial pressure upto 4 minutes after induction which is the period of maximum cardiovascular instability caused by propofol [17]. Administration of phenylephrine is claimed to improve coronary perfusion pressure, although at the expense of increasing afterload and oxygen consumption. The effect of phenylephrine is more marked on systolic than diastolic blood pressure.

Thus it may be better at maintaining organ perfusion than coronary blood flow. But in addition, concomitant venoconstriction increases venous return and left ventricular preload. In most situations, the increase in coronary perfusion pressure is more and it offsets the effect of any increase in wall tension [18]. Phenylephrine,does not change cardiac output in normal individuals but can cause a decrease in cardiac output in patients with ischemic heart disease [19]. Therefore one must be cautious in use of phenylephrine especially in high doses in coronary artery disease patients. In our study low doses of 100 microgram of phenylephrine was used than the usually recommended doses of phenylephrine for the effective management of hypotension.

It has been mentioned that propofol increases the risk of bradycardia, asystole and death. Qualitative and quantitative data analyses of data suggest that the risk of bradycardia related death during propofol anaesthesia is 1.4 per 100000 [20]. This might increase the risk of potentiating reflex bradycardia and attenuation of hypotension with use of phenylephrine.

However in this study the maximum drop in heart rate though observed in Group P patients and minimum heart rate was 38 in one occasion but the patient was otherwise hemodynamically stable. Phenylephrine induced bradycardia can be blocked by atropine.

Use of phenylephrine should be avoided in patients where cardiac output is maintained with an elevated heart rate and an optimum peripheral vascular resistance for example aortic regurgitation and aortic stenosis. In Group R patients though there were significant reduction in the heart rate but it was hemodynamically insignificant.We found oxygen saturation was within normal limit throughout the study procedure in both the study groups.

Conclusion

From our study we can aptly conclude that phenylephrine infusion in the dose of 100 microgram is effective in obtunding hypotension caused by propofol induction with minimal side effects and is a better option than crystalloid infusion.

The limitation of our study is that we have not compared different doses of phenylephrine for this purpose.

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References

1. Pamela Flood, James P. Rathmell, Steven Shafer-Pharmacology & Physiology in Anesthetic Practice: Intravenous Sedatives and Hypnotics. 2013; 5:160-161.
2. Fairfield JE, Dritsas A, Beale RJ – Hemodynamic effects of propofol: induction with 2.5 mg/kg. Br J Anaesth. 1991; 67:618-620.
3. Stephan H, Sonnatg H, Schenk HD *et al*.- Effects of propofol on cardiovascular dynamics, myocardial blood flow, and myocardial metabolism in patients with coronary artery disease. Br J Anaesth. 1986;58:969-975.
4. Reves JG, Glass SA. Nonbarbiturates intravenous anesthetics: Miller RD, Anesthesia 3 rd ed. Philadelphia: Churchill Livingstone 1990; 243-80.
5. Shearin AE, Patanwala AE, Tang A, Erstad BL. Predictors of hypotension associated with propofol in trauma patients. Journal of Trauma Nursing. January/February 2014;21(1):4-8.
6. Lavoie J, Walsh EP, Burrows FA, *et al*. Effects of propofol or isoflurane anesthesia on cardiac conduction in children undergoing radiofrequency catheter ablation for tachydysrhythmias. Anesthesiology. 1995;82 :884-887.
7. Sharpe MD, Dobkowski WB, Murkin JM, *et al*. Propofol has no direct effect on sinoatrial node function or on normal atrioventricular and accessory pathway conduction in Wolff-Parkinson-White syndrome during alfentanil/ midazolam anesthesia. Anesthesiology. 1995; 82: 888-895.
8. Ebert TJ, Sympathetic & hemodynamic effects of moderate and deep sedation with propofol in human, Anaesthesiology. 2005;103: 20-24
9. Yamakura T, Bertaccini E, Trudell JR, *et al*. Anesthetics and ion channels: molecular models and sites of action. Annu Rev Pharmacol Toxicol. 2001; 41: 23-51.
10. Ebert TJ, Muzi M, Berens R, Goff D,Kampine JP. Sympathetic response to the induction of anaesthesia in humans with propofol or etomidate. Anaesthesiology 1992;76:725-33.
11. Clayeys MA, Gepts E, Camu F. Hemodynamic changes during anaesthesia induced and maintained with propofol. Br J Anaesth 1988;60:3-9.
12. Shibata S, Matsunaga M, Oikawa M, Nitahara K, Higa K [severe hypotension after induction of general anesthesia in a patient receiving an angiotensin II receptor antagonist and an alpha blocker]. Masui 2005;54:670-72.
13. Y Dhungana, B K Bhattarai, U K Bhadani, B K Biswas, M Tripathi. Prevention of hypotension during propofol induction: a comparison of preloading with 3.5% polymers of degraded gelatin (Hemacel0 & intravenousephedrine. 2008;10(1):16-9.
14. Mohamed R El Tahan. Annals of Cardiac Anaesthesia. 14(1):30-40.
15. Imran M, Khan FH, Khan MA. Attenuation of hypotension using phenylephrine during induction of anaesthesia with propofol. 2007; 57(11): 543.

16. Turner RJ, Gatt SP, Kam PC, Ramzan I, Daley M- Administration of a crystalloid fluid preload does not prevent decrease in arterial blood pressure after induction of anesthesia with propofol and fentanyl . Br J Anaesth.1998;80:737-741.
17. Kay NH, Sear JW, Uppington J, Cockshott ID, Douglas EJ. Disposition of propofol in patients undergoing surgery. A comparison in men and women. Br J Anaesth 1986:58:1075-79.
18. Smith JS, Roizen MF, Cahalan MK, Benefiel DJ, Beaupre PN, Byrd BF, *et al*. Does anesthetic technique make a difference? Augmentation of systolic blood pressure during carotid end arterectomy: effects of phenylephrine versus light anesthesia and of isoflurane versus halothane on the incidence of myocardial ischemia. Anesthesiol 1988; 69:846-53.
19. Zaritsky AL, Chernow B. Catecholamines, sympathomimetics. In MG Ziegler, Lake CR, eds. Norepinephrine (Frontiers of Clinical Neuroscience). Baltimore MD: Wiliams & Wilkins 1984:481.
20. Tramer MR, Moore RA & McQuay HJ. Propofol and bradycardia: causation, frequency and severity. Br J Anaesth 1997;78:642-51