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Original Article

Attenuation of Hypotension using Phenylephrine during induction of anaesthesia with Propofol

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Abstract

Objective: To observe if phenylephrine mixed with propofol can attenuate hypotensive effects of propofol during induction of anaesthesia.

Methods: A total number of 135 adult ASA-I and ASA-II patients were divided into three groups. (Group A, B and C). All patients were induced with propofol 2.5 mg per kg. In Group A (control group) patients received propofol mixed with 2cc of 0.9% normal saline. Group B (study group) patients received propofol mixed with 2cc of a solution containing phenylephrine 25µg/cc (total 50µg); Group C (study group) patients received propofol mixed with 2cc of a solution containing phenylephrine 50µg/cc (total 100µg). Haemodynamic variables like systolic, diastolic, mean arterial blood pressure and heart rate were noted. Hypotension was defined as 20% decrease in baseline systolic blood pressure recorded before induction of anaesthesia.

Results: Phenylephrine in a dose of 100 micrograms attenuated the drop in systolic blood pressure. However phenylephrine in a dose 50 micrograms did not effectively prevent anticipated drop in SBP.

Conclusion: Phenylephrine in doses of 100 micrograms effectively attenuates anticipated hypotension upon induction of general anaesthesia with propofol (JPMA 57:543:2007).

Introduction

Propofol is one of the most recent intravenous anaesthetic agents being used in clinical practice. Propofol has been used for induction and maintenance of anaesthesia, for sedation to supplement regional anaesthesia as well as sedation of patients in ICU.[1]

Propofol, when used for induction of anaesthesia in shorter procedures, results in significantly quicker recovery and earlier return of psychomotor function as compared to thiopental and methohexital, irrespective of the agent used for maintenance of anaesthesia.[2]

Induction with propofol has also some untoward effects. These include pain on injection, myoclonus, apnea and rarely thrombophlebitis. However decrease in the systemic blood pressure associated with induction of anaesthesia with propofol is its most significant side effect.[1]

Direct myocardial depression and decreased systemic vascular resistance have been implicated as important factors in producing cardiovascular depression. These effects are dose dependent. In addition to arterial vasodilatation, propofol produces venodilation which further contributes to its hypotensive effect.[3] The smaller increase in heart rate with propofol may account for the larger decrease in arterial pressure than with an equipotent dose of thiopental.[4] Age enhances the cardio-depressant response to propofol and dosage adjustments are required in the elderly.[5] In fact in some elective clinical scenarios, this hypotensive effect of Propofol has been exploited to use it as a drug of choice for controlled hypotensive technique.[6] This hypotensive effect of propofol is not desirable mostly and particularly in sick patients and older age group patients.

A number of techniques have been tried to counteract the hypotensive effects of propofol, for example slow administration of drug, preloading, and administration of vasoactive drugs to raise BP.[1]

Phenylephrine is a synthetic non-catecholamine that stimulates principally alpha-1 adrenergic receptors by a direct effect. Only a small part of the pharmacologic response is due to its ability to release nor-epinephrine (indirect acting) and it has a minimal effect on beta-adrenergic receptors.

Phenylephrine, 50 to 200 micrograms intravenous, is often administered to adults to treat fall in blood pressure that accompanies sympathetic nervous system blockade produced by a regional anaesthetic technique and peripheral vasodilatation that accompanies administration of injected or inhaled anaesthetics.[7]

The objective of this study was to evaluate efficacy of phenylephrine by mixing it in two different doses to counteract the anticipated hypotensive effects of propofol during induction of anaesthesia. Hypotension is defined as 20% decrease in baseline systolic blood pressure recorded before induction of anaesthesia.[8]

We used LMA (Laryngeal mask airway) to maintain the airway in our study as its cardiovascular response upon insertion is not significant. Thus airway management was less likely to impede in depicting the actual response of drugs given for induction of anaesthesia.[9]

Patients and Methods

This randomized controlled trial was performed at Aga Khan University Hospital after approval from Ethical Review Committee. Written informed Consent was taken from all the subjects. The study included 135 patients divided into 3 groups randomly each consisting of 45 patients. Group A received propofol mixed with 2cc of 0.9% normal saline .Group B were given propofol mixed with 50µg (2cc) of phenylephrine in concentration of 25µg/cc. Group C received propofol mixed with 100µg (2cc) of phenylephrine in a concentration of 50µg/cc .

Randomization was done with closed envelopes technique. Drug administration and data recording was done by two separate persons blinded to the study group. Inclusion criteria was ASA group I & II, patients aged between 15-65 years and patients undergoing elective surgery requiring GA and LMA insertion. ASA group III & IV, surgery requiring general anaesthesia with endotracheal tube insertion, patients with known cardiovascular disease and hypersensitivity to propofol, failure to insert LMA in first attempt, patients fasting more then 10 hours, were excluded from study.

After arrival of the patient in OR, routine monitoring was started including blood pressure, oxygen saturation, ECG and end tidal CO_2. Baseline reading of blood pressure, heart rate and saturation were taken 5 minutes after the application of monitors. Patients were pre-oxygenated for 3 minutes using facemask at 4 L / min O_2 with Lack circuit.

Anaesthesia was then induced using Propofol (mixed with study drug) given over 20 seconds. Maintenance was with O_2 \ N_2O mixture and isoflurane 2%. Ventilation was gently assisted using face mask and maintaining $ETCO_2$ between 30-40 mmHg. After proper jaw relaxation LMA was inserted and connected to the circuit. Patients who failed successful LMA insertion in first attempt were excluded from the study. Breathing was gently assisted until the restoration of spontaneous Breathing. Systolic, diastolic, MAP, heart rate and SpO_2 were monitored from time zero (From start of induction) and then at 1 minute interval until 6 minutes.

Data was collected and analyzed using the software Epi-data and SPSS version 10 for statistical analysis. Demographic data was analyzed using Epi-data and comparison of means was done. For haemodynamic parameters SPSS was used and repeated measures ANOVA was applied. Overall incidence of hypotension was represented in terms of percentage and groups were compared using the 'comparison of proportions'. P-value was calculated and documented.

Results

The total numbers of patients studied were 135, with 45 in each group. Two patients in Group A and one in group B were excluded from analysis as they became hypotensive (Systolic blood pressure < 75mmHg) requiring intervention. The mean age of the study group was 33.76 ± 9.75. There were no statistically significant differences between the groups with respect to age, weight and height (Table 1).

Heart rate, systolic, diastolic, mean arterial pressure and SpO_2 were compared at 1 minute interval with baseline. We compared mean values of group B and C (Study group) with group A (Control group) to note any significant difference. Study groups (B & C) were also compared with each other.

Statistically significant difference from baseline values was observed in mean systolic blood pressure at minute 4 when group A was compared with group B (Table 2) , while this difference was statistically significant from minute one to four when group A was compared with group C ($p < 0.05$) . Thus in group C systolic blood pressure did not fall significantly for a longer period of time. Similar comparison was done for mean diastolic blood pressure and no significant difference was found between group A and B. Statistically significant difference was found at minute two and three between group A and C. Mean arterial pressure was also not significantly different between groups A and B but the difference was statistically significant from minute 2 to 4 between groups A and C ($p < 0.05$)

In contrast, change in heart rate was significant in Group B and lasted for a longer period i.e. from minute one to four as compared to that in group C which was a slightly shorter period from minute 1 to 3 (Table 2). Results depicted a greater decrease in heart rate in group B ($p < 0.05$)

We also compared both study groups with each

Table 1. Comparison of demographic data between groups.

	Control Group A (n=43)	Study Group B (n=44)	Study Group C (n=45)
Age (years)	33.84 ± 10.11	32.39 ± 8.15	35.69 ± 10.51
Sex (Male/Female)	21/22	25/19	24/21
Height (cm) *	161.43 ± 7.65	163.07 ± 5.31	159.76 ± 6.42
Weight (kg) +	64.98 ± 10.70	65.25 ± 10.70	63.60 ± 10.51

Values are expressed as means ± Standard deviation
n = Numbers
* Centimeters
+ Kilograms

Table 2. Comparison of Haemodynamics data of study groups (B&C) with control group A

Time	Variables	Group A	Group B	Group C	P value group B	P value group C
5 minute	H.R*	89.44± 12.26	99.02±84.50	83.42 ±13.13	0.508	0.051
after	SBP+	130.60±15.33	131.33±11.91	128.16±6.14	0.800	0.94
arrival	DBP++	81.84± 11.29	83.76±9.96	79.82±10.46	0.404	0.94
	MAP#	98.10±12.22	99.61±10.05	95.93±11.61	0.525	0.377
Before	H.R	88.63±13.79	84.80±12.40	83.36±12.97	0.183	0.068
induction	SBP	129.63±14.91	130.73±12.26	125.0±15.71	0.64	0.185
	DBP	80.28±10.96	82.25±11.21	78.22±9.66	0.410	0.352
	MAP	96.64±11.64	98.41±1078	93.81±10.95	0.465	0.243
Minute	H.R	90.19±15.31	75.80±12.63	74.22±17.07	0.000	0.000
	SBP	114.02±15.54	118.89±12.26	132.07±17.70	0.111	0.000
1	DBP	103.02±12.34	75.18±11.01	83.24±12.07	0.29	0.387
	MAP	106.6±12.61	89.75±10.65	99.51±12.96	0.284	0.655
Minute	H.R	92.91±11.51	81.30±12.25	72.71±16.61	0.000	0.000
	SBP	112.14±10.86	113.43±12.18	125.07±18.11	0.603	0.000
2	DBP	72.12±12.11	71.20±1099	78.07±11.76	0.714	0.02
	MAP	85.46±10.74	85.28±10.68	93.73±13.30	0.939	0.02
Minute	H.R	94.02±13.92	86.25±11.34	80.73±14.49	0.005	0.000
	SBP	110.98±12.95	106.50±12.18	121.24±17.12	0.072	0.004
3	DBP	67.56±11.50	66.91±9.89	77.11±11.37	0.77	0.007
	MAP	82.03±10.98	80.11±9.38	91.82±12.99	0.38	0.002
Minute	H.R	93.93±13.71	88.02±8.51	88.24±13.42	0.018	0.053
	SBP	110.35±11.72	105.35±9.26	116.69±17.12	0.023	0.047
4	DBP	67.19±11.12	65.30±10.38	71.58±11.34	0.437	0.083
	MAP	81.57±11.24	78.57±9.49	86.61±12.57	0.181	0.050
Minute	H.R	91.63±14.72	85.77±8.59	88.09±14.52	0.077	0.260
	SBP	108.0±10.85	105.93±9.10	110.80±13.01	0.309	0.444
5	DBP	67.02±11.46	63.86±9.31	71.13±19.21	0.164	0.225
	MAP	80.73±10.39	77.88±8.68	84.36±16.61	0.172	0.221
Minute	H.R	88.81±12.37	88.14±12.32	90.45±13.92	8.44	0.600
	SBP	107.53±9.19	107.82±9.10	110.40±10.81	0.908	0.231
6	DBP	64.66±10.39	63.68±6.35	68.40±9.71	0.697	0.115
	MAP	78.95±9.65	78.39±6.38	82.40±9.53	0.811	0.128

* H.R : Heart rate in beats / minute Values expressed means ± Standard deviation
+SBP : Systolic blood pressure in millimeter of mercury.
++DBP : Diastolic blood pressure in millimeter of mercury.
MAP : Mean arterial pressure in millimeter of mercury.

other. Values for Systolic blood pressure were significantly different between the two groups. This difference was found from minute 1 to 4 ($p < 0.05$) with better control of systolic blood pressure in group C. The diastolic blood pressure values had a significant difference from minute 1 to 6 ($p < 0.05$). Mean arterial pressure was significantly different from minute 1 to minute 5 ($p < 0.05$). The difference in heart rate was significant only at minute 2 and 3. Values of SpO_2 were similar in all groups.

Hypotension was defined as 20% decrease in systolic blood pressure from baseline value recorded before induction of anaesthesia. The frequency of hypotension in our study cases was 43% (59/135), with group A having 51%, group B 56 % ($P < 0.8$) and group C only 20% ($P < 0.004$). Hypotension in group A and B closely approximate the values given in phase 4 study done by Hug et al on 25,000 patients[8], which had a figure of 55.7% hypotension. Mean drop in SBP was 17.11% in group A , 20.16 % in group B and 11.71 % in group C. Fall of systolic blood pressure (< 20 % from baseline) in Group A started at minute 2, from minute 3 in group B which continued to 5 minutes (Control group).

Rise in systolic blood pressure from baseline was also analyzed. In group A, 13.9% (Total 6) patients, 9% in

group B and 57.57 % in group C had increased systolic blood pressure. Almost all occurred at 1 and 2 minute after induction. Maximum rise in systolic pressure was 38.79%, in group C, 16.5% in group A and 2.5% in group B.

Discussion

Propofol`s direct myocardial depression and reduction in systemic vascular resistance have been implicated as important factors in producing cardiovascular depression. In addition to arterial vasodilatation, propofol produces venodilation due both to a reduction in sympathetic activity and a direct effect on the vascular smooth muscle, which further contributes to its hypotensive effect.[10] 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.[11] Propofol alters the baroreflex mechanism, resulting in a relatively smaller increase in heart rate for a given decrease in arterial pressure.[12] Study conducted by Clayes et al suggested that the major haemodynamic effect of propofol is a decrease in arterial pressure as a result of decrease SVR.[13] This decline in blood pressure may be more severe if patient is already on vasodilator therapy such as a-1 blockers.[14] Propofol has been considered as one of the important predictors of hypotension[15] therefore vasoconstriction is indicated during episodes of systemic hypotension, especially in cases where it is stimulation or drug-induced vasodilatation as with propofol .

A number of techniques have been tried to counteract the hypotensive effects of propofol, for example slow administration of the drug, preloading, and administration of different drugs to elevate BP.[16] Vasoconstrictors are useful adjuncts in the prevention and treatment of ischaemia owing to their ability to increase systemic blood pressure. In a study done by Ishiyama T et al ephedrine was given just before induction to obtund the hypotensive response of propofol induction.[17]

We used phenylepehrine with propofol to attenuate its hypotensive effect during induction of anaesthesia. The observation in our study suggests that addition of phenylepehrine in a dose of 50 micrograms was insufficient to completely obtund the hypotensive effects; however, the dose of 100 micrograms was very effective. Phenylepehrine in 100 micrograms dose sustained systolic blood pressure up to 4 minutes after induction which is the period of maximum cardiovascular instability caused by propofol.[18]

Cardiovascular effects of phenylepehrine are mentioned mainly in prevention of spinal induced hypotension and to preserve brain perfusion during carotid endarterectomy. In obstetric patients phenylephrine prevented spinal-induced hypotension decreases heart rate and cardiac output while restoring systolic, mean, and diastolic blood pressure.[19] However these studies were conducted in most obstetrical patients, who are young, healthy with no cardiac issues. In carotid endarterectomy, it may induce segmental wall abnormalities detected by TEE. However this occurs with indiscriminate use of this drug. Administration of phenylephrine is claimed to improve coronary perfusion pressure, although at the expense of increasing after load and oxygen consumption. Our data shows that the effect of phenylepehrine is more marked on systolic then diastolic BP. Thus it may be better at maintaining organ perfusion then coronary blood flow, but in addition, concomitant venoconstricton 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.[20]

The adverse effects of phenylepehrine on cardiovascular systems are also well documented but most of these effects were mentioned with its use as a topical agent for example in ophthalmic preparations where very potent solutions are used.[21]

Epicardial vessels, which possess mainly alpha-1 receptors, contribute only 5% to the total resistance of the coronary circulation; therefore, alpha-1 agonists such as phenylephrine have little influence on coronary resistance.[22] Phenylephrine, like methoxamine, does not change cardiac output in normal individuals but can cause a decrease in cardiac output in patients with ischaemic heart disease.[23] Stimulation of alpha-1 receptors in the heart by phenylephrine may contribute to the production of cardiac dysrhythmias during halothane anaesthesia.[24] Therefore one must be cautious in use of phenylepehrine especially in high doses in coronary artery disease patients. We used moderately low doses in our study then the usually recommended doses of phenylephrine for the treatment of hypotension.

In our study 57 % patients in group C had rise in SBP from baseline. Maximum increase was 38% from baseline. Most of patients had increase in SBP at 1st and 2nd minute with greatest increase in 2nd minute. However pressure returned to baseline later on. This finding needs consideration and exercise caution in patients who are unpremedicated, anxious, given inadequate induction doses and inadequately treated hypertensive patients.

It has been mentioned that propofol increases the risk of bradycardia, asystole, and death, qualitative and quantitative analyses of data suggest that the risk of bradycardia-related death during propofol anaesthesia is 1.4 per 100,000.[25] This might increase the risk of potentiating reflex bradycardia and attenuation of hypotension with use

of phenylephrine. However in our study the maximum drop in heart rate was 50% from baseline and minimum heart rate was 45/minute. This finding was observed in group C. In group B maximum drop was 38% from baseline. Minimum heart rate in this group was 52/minute. The decrease in heart rate was not accompanied by decrease in blood pressure. Phenylephrine induced bradycardia can be blocked by atropine. Use of phenylephrine should be avoided in patients where cardiac output is maintained on elevated heart rate and an optimum peripheral vascular resistance for example aortic regurgitation and aortic stenosis.

Overall incidence of hypotension was slightly more in group B when compared with group A i.e. 56% vs. 51% but episodes of hypotension were less in first 2 minutes in group B as compared to A (12 vs.19), thereafter number of patients getting hypotensive surpasses as in group A. This could be due to the fact that a small dose of phenylephrine prevented hypotension initially but this small dose was consumed rapidly after which hypotensive effects of propofol predominated. However the incidence is not statistically significant.

Conclusion

The observations of the presented study period the effectiveness of phenylephrine in attenuation of anticipated hypotension upon anaesthesia induction with propofol. We found that phenylephrine in a dose of 100 microgram is more effective then 50 microgram to prevent hypotension with propofol induction.

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