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Brief communication (Original)

Ephedrine and propofol for induction of general anesthesia can decrease intraoperative hypothermia in patients undergoing plastic and breast surgery: a randomized, controlled trial

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Background: Ephedrine has vasoconstrictive and mild β-adrenergic agonist effects that may be able to decrease intraoperative core temperature hypothermia. However, its efficacy is still unclear.
Objectives: To determine the efficacy of ephedrine given during induction to maintain core temperature during plastic and breast surgery under general anesthesia.
Materials and Methods: A prospective, randomized, double-blinded study was approved by our Institutional Review Board and registered with the Thai Clinical Trials Registry as TCTR20141212002. We randomly assigned 30 patients to receive mixture of propofol and ephedrine (ephedrine group, n = 15) or a mixture of propofol and normal saline (control group, n = 15) for induction of general anesthesia. The tympanic temperature (core temperature before intubation), esophageal temperature (core temperature after intubation), index temperature (peripheral temperature), systolic and diastolic blood pressure were compared between groups and baselines.
Results: During surgery, patients in ephedrine group showed better esophageal temperature maintenance than those in the control group. Whereas systolic blood pressure in ephedrine group was significantly higher than in the control group in early phase after induction.
Conclusions: A bolus dose of ephedrine given during induction can decrease core temperature loss during plastic and breast surgery under general anesthesia.

Keywords: Ephedrine, general anesthesia, hypothermia, temperature

Intraoperative hypothermia is well known to cause various complications during both intraoperative and postoperative periods [1-3]. Much effort has been devoted to improving core temperature preservation. Because the main mechanism for the first hour of heat loss during general anesthesia is redistribution of heat from the central core to the periphery [4], many approaches have been attempted to reduce vasodilation and, by consequence, decrease core temperature loss [5]. Ephedrine stimulates norepinephrine release and also has mild β-adrenergic agonist effects, which may be able to counteract vasodilation. Its duration of action also provides the possibility for it to be administered as a bolus dose. An admixture of ephedrine and propofol had demonstrated more hemodynamic stability when administered for induction [6, 7]. Therefore, the mixture may be able to both preserve core temperature and reduce hypotension caused by propofol. This study was designed to determine the efficacy of single bolus dose of ephedrine given during induction of general anesthesia on preserving esophageal temperature.

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Materials and methods

The study was approved by Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine Ramathibodi Hospital, Mahidol University and protocol of this study was registered in Thai Clinical Trials Registry and coded as TCTR20141212002. We recruited 30 patients in Ramathibodi Hospital aged 18–70 years old with an American Society of Anesthesiologist physical status I–III who were scheduled to undergo plastic or breast

surgery with expected duration of surgery longer than 120 min. Signed written informed consent was obtained from all patients. Patients with a tympanic temperature more than 37.5°C, blood pressure at time of induction more than 140/90 mmHg, BMI more than 30, thyroid disease, receiving medications for hypertension, with a risk of aspiration or expected difficult airway were excluded. The patients with actual surgery time less than 90 min, hand, wrist, forearm, or intraoral surgery were also excluded. The patients were randomized into an ephedrine group (n = 15) and control group (n = 15) using a computer-generated randomization list in a sealed envelope.

All patients received 7.5 mg of midazolam orally before the scheduled time for surgery. Warmed Ringer's acetate (41°C) was used for intravenous fluid supplementation in all patients. A skin temperature probe was attached to the palmar side of index finger of the noninfused arm and index temperature was recorded. At time of induction all patients received intravenous 50 μg of fentanyl. General anesthesia was induced with a mixture of 2 mg/kg of propofol and 12 mg (6 mg/mL, total 2 mL) of ephedrine in ephedrine group and mixture of 2 mg/kg of propofol and 2 mL of normal saline in the control group. All induction agents were prepared by another anesthesiologist who was not involved in data collection and analysis. After induction patients in both groups were ventilated with 2% sevoflurane and oxygen. Atracurium 0.5 mg/kg was given and intubation was performed 3 min later. Anesthesia was maintained with 1% sevoflurane in FiO_2 0.5 oxygen/nitrous oxide during study and depended on attending anesthesiologist thereafter. Additional doses of fentanyl, atracurium, and rate of Ringer's acetate infusion were also at the discretion of the attending anesthesiologist. Before intubation, tympanic temperature, index temperature, blood pressure were recorded preinduction (Pre-in) and at 2.5 min after induction (Post-in). Immediately after intubation (T0), an esophageal temperature probe was installed and esophageal temperature, tympanic temperature, index temperature, and blood pressure were recorded. After intubation esophageal temperature, index temperature, and blood pressure were recorded at 15 min intervals (T0, T1, …, T120). If during the study, systolic blood pressure fell below 90 mmHg then 300 mL of Ringer's acetate would be loaded and 2.5 min later blood pressure would be remeasured. If systolic blood pressure remained below 90 mmHg, the patient would be recorded as having hypotension. Then 3 mg of ephedrine would be given and blood pressure would be remeasured at every 2.5 min until systolic blood pressure rose higher than 90 mmHg. If esophageal temperature fell below 35°C, the patient would be warmed using a forced-air warmer. If ephedrine was given because of hypotension or a forced-air warmer was applied, data collected subsequently would not be analyzed. At 90 min and 120 min after intubation, the amount of intravenous fluid infused, blood loss, total fentanyl, and ephedrine given were recorded. Data collection ceased at 120 min after intubation or after skin suturing was completed. The attending anesthesiologist collected all data. The primary outcome was to demonstrate a difference in esophageal temperature between the groups.

Based on a previous study [8], sample size was calculated with an α error of 0.5 and power of 80%. A sample size power calculation determined that 12 patients were needed in each group. A further 20% of participants were added for dropout, resulted in 15 patient participants per group and total of 30 participants.

All results were analyzed using IBM SPSS Statistics for Windows (version 20.0, IBM Corp, Armonk, NY, USA). According to the results from a Shapiro–Wilk normality test, parametric data (e.g. age, body weight, height, all measured temperatures) were summarized by mean and standard deviation, where nonparametric data (e.g. blood loss and anesthesia time) by median and range, and categorical data by number with percentage. Parametric and nonparametric data were compared using a *t* test and Mann–Whitney *U* test respectively, whereas categorical data were compared using a chi-squared or Fisher's exact test. Interval parametric data (e.g. SBP, DBP, temperatures) were compared using a repeated measures ANOVA. $P < 0.05$ was considered significant.

Results

All demographic and perioperative data are shown in **Table 1**. All operations exceeded 90 min postintubation, but only 22 operations, 11 in control group and 11 in ephedrine group, had exceeded 120 min. During the 90–120 min postintubation period, 3 patients in control group had hypothermia, forced-air warmer was applied and temperature was not further recorded. One of the 3 patients also had hypotension, 12 mg of ephedrine was administered and blood

pressure was not further recorded. Because there was change in sample size to less than calculated after T105, data at T105 and T120 are listed, but not analyzed. No significant difference in patient characteristics, operating room temperature, operation time, blood loss and total amount of fentanyl were found. However, total intravenous fluid was significantly less in the ephedrine group than in the control group at both 90 min (T90) and 120 min (T120) after intubation. No patient developed hypotension in the first 90 min, but 1 patient in the control group had hypotension during the 90 to 120 min period. No significant difference in preinduction blood pressure, tympanic, or index temperature was found.

From after induction to the immediate postintubation period, tympanic membrane temperature did not change significantly from baseline at preinduction in either group. After intubation esophageal temperature gradually declined in both groups and became significant when compared with immediate post-intubation (T0) after T15 for control group, and T30 for ephedrine group. When compared between groups, esophageal temperature was significantly higher in the ephedrine group start from T60 to T90. Index temperature, when compared between groups, was significantly higher in the ephedrine group only at post-induction 2.5 min and T0. The index temperature was highest at T15 in the ephedrine group and at T30 in control group (**Table 2**).

After induction systolic blood pressure in the ephedrine group tended to rise and became significantly higher at T0 then significantly fell to below preinduction from T15 to T30. In control group, systolic blood pressure was significantly lower than preinduction at 2.5 min after induction, from T15 to T45, and at T75. When compared between groups, significant differences in systolic blood pressure were found from 2.5 min after induction to T15. Diastolic blood pressure also showed similar pattern (**Table 3, Figures 1-3**).

Table 1. Patient characteristics and preoperative data

	Control (n = 15)	**Ephedrine (n = 15)**	***P***
Sex, female/male, n	11/4	12/3	>0.999
Age, y	33.8 ± 11.3	30.3 ± 9.9	0.38
BMI	21.9 ± 3.2	21.8 ± 3.8	0.87
Operating room temperature, °C	21.1 ± 0.9	20.8 ± 1.2	0.42
Anesthesia time, min (median [range])	145 [95–290]	135 [90–405]	0.39
At 90 min			
Hypotension, n	0	0	–
IV fluid, mL	963 ± 418	660 ± 219	0.02*
Blood loss, mL (median [range])	20 [5–500]	40 [5–250]	0.41
Fentanyl, μg (median [range])	100 [50–250]	100 [50–150]	0.38
At 120 min			
Hypotension, n	1	0	>0.999
IV fluid, mL	1235 ± 578 (n = 11)	762 ± 245 (n = 11)	0.02*
Blood loss, mL (median [range])	20 [5–500] (n = 11)	50 [5–250] (n = 11)	0.52
Fentanyl, μg (median [range])	100 [50–300] (n = 11)	100 [50–150] (n = 11)	0.22

Values are the mean ± SD, unless specified, *$P < 0.05$ statistical significance

Table 2. Comparing temperature between groups

Temperature	Control (n = 15)	Ephedrine (n = 15)	*P*	Temperature	Control (n = 15)	Ephedrine (n = 15)	*P*
Tympanic			0.38	Index			0.03*
Pre-in	36.6 ± 0.45	36.7 ± 0.5	0.55	Pre-in	26.7 ± 2.1	27.99 ± 2.49	0.15
Post-in	36.4 ± 0.42	36.7 ± 0.5	0.099	Post-in	27.9 ± 2.6	30.53 ± 2.55	0.01*
T0	36.4 ± 0.7	36.5 ± 0.5	0.83				
Esophageal			0.03*	T0	29.7 ± 2.8	31.96 ± 2.52	0.03*
T0	36.3 ± 0.3	36.4 ± 0.4	0.51				
T15	35.9 ± 0.4	36.2 ± 0.4	0.13	T15	32.7 ± 1.7	33.31 ± 2.45	0.47
T30	35.8 ± 0.5	36.0 ± 0.4	0.11	T30	33.0 ± 1.8	33.05 ± 1.89	0.97
T45	35.7 ± 0.4	35.9 ± 0.4	0.09	T45	32.3 ± 2.6	32.80 ± 1.70	0.49
T60	35.5 ± 0.4	35.9 ± 0.4	0.02*	T60	30.5 ± 3.8	32.49 ± 2.19	0.06
T75	35.5 ± 0.4	35.9 ± 0.4	0.01*	T75	29.8 ± 4.1	31.60 ± 2.48	0.16
T90	35.4 ± 0.4	35.9 ± 0.4	0.006*	T90	28.8 ± 4.3	31.13 ± 2.90	0.09
T105	35.6 ± 0.4 (n = 8)	35.9 ± 0.5 (n = 11)		T105	29.3 ± 3.5 (n = 8)	31.78 ± 3.29 (n = 11)	
T120	35.6 ± 0.4 (n = 8)	35.9 ± 0.6 (n = 11)		T120	29.7 ± 4.3 (n = 8)	32.62 ± 2.21 (n = 11)	

Values are the mean ± SD, **P* < 0.05 statistical significance, Pre-in = pre-induction, Post-in = post-induction 2.5 min, T0, 15, 30, …, 120 = At 0, 15, 30, …, 120 min after intubation

Table 3. Comparing systolic and diastolic blood pressure between groups

Systolic pressure	Control (n = 15)	Ephedrine (n = 15)	*P*	Diastolic pressure	Control (n = 15)	Ephedrine (n = 15)	*P*
			0.006*				0.046*
Pre-in	120.4 ± 16.1	120.9 ± 13.5	0.92	Pre-in	72.9 ± 7.6	75.4 ± 11.7	0.49
Post-in	91.0 ± 10.6	125.5 ± 14.5	<0.001*	Post-in	51.1 ± 8.4	73.3 ± 12.7	<0.001*
T0	121.1 ± 19.9	142.5 ± 25.9	0.02*	T0	78.9 ± 16.7	85.6 ± 17.7	0.30
T15	97.0 ± 10.0	111.0 ± 11.7	0.001*	T15	59.5 ± 9.2	65.5 ± 14.7	0.19
T30	104.4 ± 15.4	109.5 ± 10.7	0.30	T30	68.1 ± 12.4	63.7 ± 10.8	0.30
T45	107.7 ± 15.2	113.7 ± 15.9	0.30	T45	70.2 ± 15.4	67.1 ± 10.5	0.53
T60	109.9 ± 12.3	113.01 ± 12.5	0.49	T60	70.3 ± 14.5	69.1 ± 12.6	0.81
T75	108.3 ± 12.5	120.5 ± 19.2	0.048*	T75	70.6 ± 12.1	73.2 ± 12.4	0.45
T90	113.2 ± 15.4	118.6 ± 12.1	0.30	T90	72.7 ± 15.3	70.3 ± 13.7	0.65
T105	114.5 ± 16.6 (n = 10)	114.9 ± 13.0 (n = 11)		T105	74.9 ± 11.7 (n = 10)	67.6 ± 10.7 (n = 11)	
T120	118.0 ± 14.6 (n = 10)	112.9 ± 11.8 (n = 11)		T120	76.3 ± 14.6 (n = 10)	66.5 ± 12.5 (n = 11)	

Values are the mean ± SD, **P* < 0.05 statistical significance, Pre-in = pre-induction, Post-in = post-induction 2.5 min, T0, 15, 30,…, 120 = At 0, 15, 30,…, 120 min after intubation

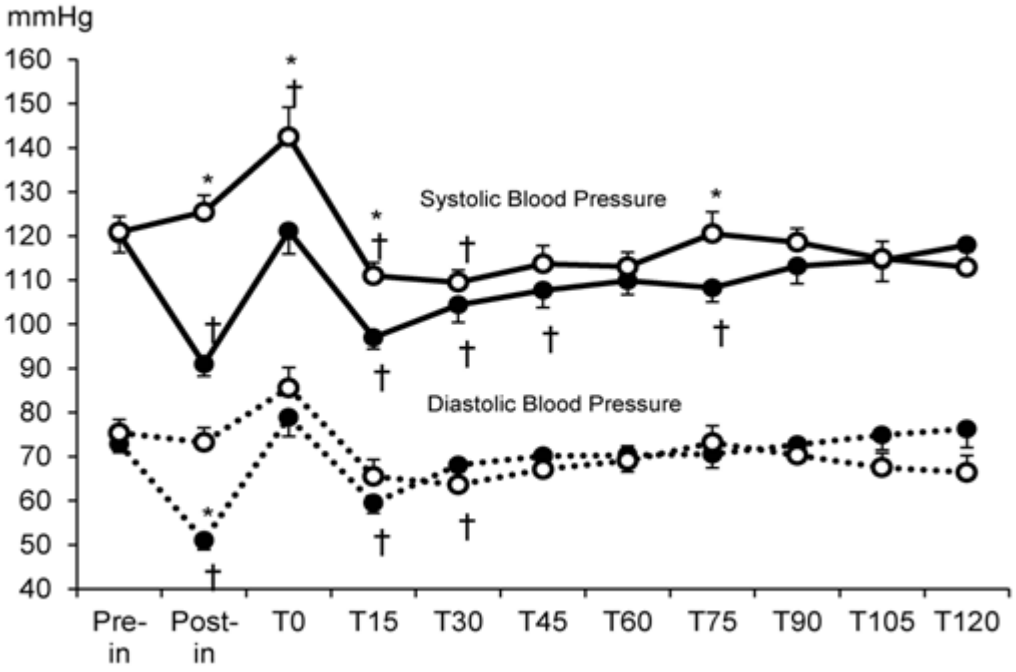

Figure 1. Systolic blood pressure and diastolic blood pressure by group. Open circles indicate the ephedrine group, and solid circles indicate the control group. Data are mean with standard error of mean, **P* < 0.05 (between groups), †*P* < 0.05 (within group from Pre-in), Pre-in = pre-induction, Post-in = post-induction 2.5 min, T0, 15, 30, …, 120 = at 0, 15, 30, …, 120 min after intubation.

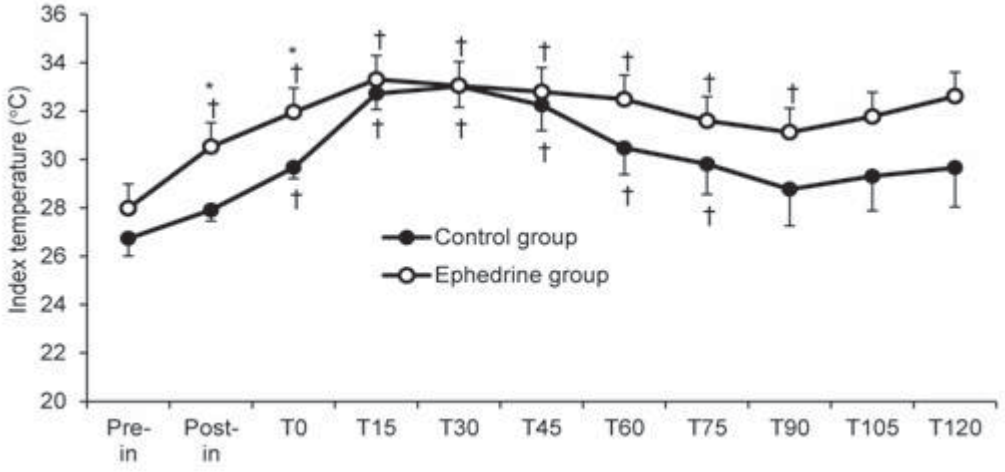

Figure 2. Index temperature by group. Open circles indicate the ephedrine group, and solid circles indicate the control group. Data are mean with standard error of mean, **P* < 0.05 (between groups), †*P* < 0.05 (from Pre-in), Pre-in = pre-induction, Post-in = post-induction 2.5 min, T0, 15, 30, …,120 = at 0, 15, 30, …, 120 min after intubation.

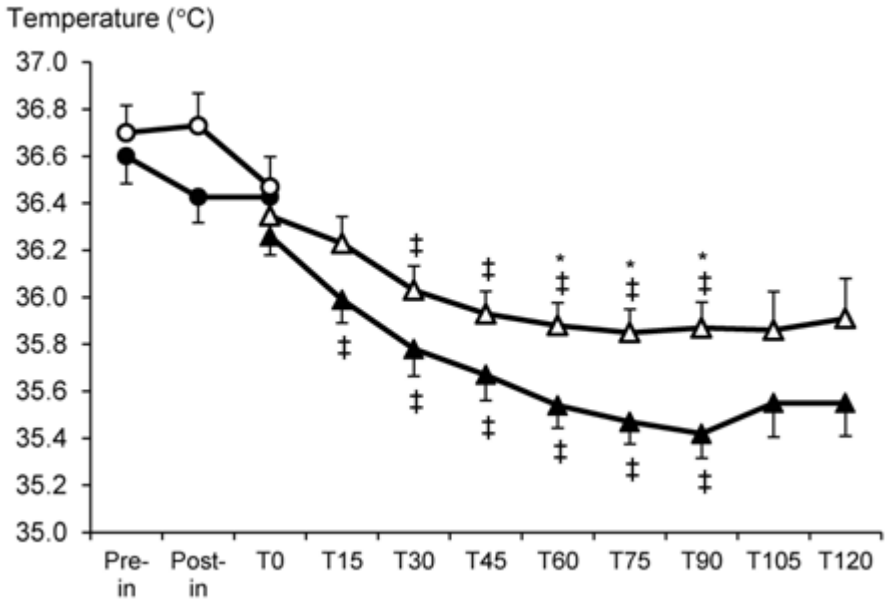

Figure 3. Tympanic and esophageal temperature by group. Tympanic temperatures are represented by circles and esophageal temperatures are represented by triangles. Open symbols indicate the ephedrine group, and solid symbols indicate the control group. Data are mean with standard error of mean, *$P < 0.05$ (between groups), †$P < 0.05$ (from Pre-in by tympanic temperature) none, ‡$P < 0.05$ (from Post-in by esophageal temperature), Pre-in = pre-induction, Post-in = post-induction 2.5 min, T0, 15, 30, …, 120 = at 0, 15, 30, …, 120 min after intubation.

Discussion

The current study suggested that ephedrine administered as bolus dose during induction is effective in preventing core temperature loss in plastic and breast surgery. The mixture of 12 mg of ephedrine and 2 mg/kg of propofol used results in a mild increase in blood pressure after induction, which was only significant immediately after intubation, and then fell below baseline to a lesser degree when compared with a mixture of propofol and normal saline.

Previously, successful treatment of cyclical hypothermia with ephedrine had been reported [9]. Jo et al. also reported the core temperature conserving property of ephedrine when infused continuously after intubation in spine surgery with no significant hypertension [8].

The increase in index temperature after induction in both groups suggested the effect of heat redistribution. Faster time-to-peak in the ephedrine group suggests an increase in cardiac output while the early decline suggests a vasoconstriction effect. Both esophageal and index temperature tended to be higher in the ephedrine group. This might be partly result from increasing metabolism or from the β-adrenergic agonist effect of ephedrine [10].

More stable hemodynamics have been reported for combined ephedrine with propofol. Less hypotension with no significant hypertension was found when 0.15 mg/kg ephedrine was combined with 2.5 mg/kg of propofol, and 3 μg/kg of remifentanil [7]. A similar profile can be seen in this study except for the significant increase in blood pressure at immediate after intubation, which might result from the difference in anesthetic agents and doses.

Some of limitations of this study should be considered. An esophageal temperature probe was not fitted before intubation because of patient discomfort. By using tympanic membrane temperature, the trend of core temperature change can be demonstrated, but may not be a reliable substitute for baseline. The amount of fluid infused was determined by the attending anesthesiologist. Therefore, all fluid was warmed to 41°C to minimize the effect of cold fluid. Finally, plastic surgery varies in sites of operation and exposures may affect heat loss and skin temperature monitoring.

Conclusion

Induction of general anesthesia with mixture of ephedrine and propofol can decrease core temperature

loss during plastic and breast surgery compared with propofol alone.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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