Original Article

Single Bolus Intravenous Ephedrine Attenuates Reduction of Core Body Temperature in Patients Undergoing Spinal Anesthesia for Arthroscopic Knee and Ankle Surgery

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Objective: To determine the efficacy of a single bolus ephedrine on body temperature reduction attenuation during arthroscopic knee and ankle surgery under spinal anesthesia.

Materials and Methods: The present study was a single-center prospective randomized clinical trial. Patients undergoing arthroscopic ankle or knee surgery were randomized to receive a single intravenous bolus dose of placebo (normal saline) or ephedrine 9 milligrams (mg) just after a subarachnoid injection for spinal anesthesia. Tympanic membrane temperature and blood pressure were recorded at time points. Two-way repeated-measures ANOVAs was performed to analyze the difference of temperature at time points compared with before performing spinal block as primary outcome.

Results: Forty patients were randomized, and 34 patients were included in outcome analysis (control n=18 and ephedrine n=16). Patients in the ephedrine group demonstrated better body temperature preservation. The earliest significant effect could be seen 7.5 minutes after the spinal block (control group –0.32±0.39°C and ephedrine group –0.24±0.5°C, p=0.007). The ephedrine effect on blood pressure was subtle.

Conclusion: For patients undergoing knee or ankle arthroscopic surgery, a single bolus 9 mg of ephedrine given intravenously just after the subarachnoid injection for spinal anesthesia can preserve core temperature.

Trial registration: ClinicalTrials.gov, NCT02948920

Keywords: Ephedrine, Heat, Hypothermia, Spinal anesthesia, Temperature

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Spinal anesthesia produces sympathectomy that results in vasodilatation below the level of block. Apart from hypotension, which is common, it is frequently accompanied by hypothermia. Many mechanisms contribute to hypothermia such as increased heat loss to environment due to loss of superficial vasoconstriction and mixing of cold blood from superficial and warm blood from core compartment by peripheral vasodilatation[1-3]. Since the adverse effects of core temperature hypothermia are detrimental, various measures to prevent or reduce heat loss were studied with varying degrees of success. Ephedrine, a familiar drug for perioperative hypotension, acts both directly and indirectly as sympathomimetic agent. Its vasoconstriction effect counteracts vasodilatation from spinal block, together with its thermogenic effect reduce heat loss and theoretically may help preserve body temperature[4,5]. The present study was a single-center randomized controlled trial aimed to determine the efficacy of core temperature preserving effects of ephedrine administered as a single bolus dose to patients under spinal anesthesia for lower limb arthroscopic surgery.

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Materials and Methods

The present study was approved by the institutional ethical committee. The patients were enrolled between September 2016 and July 2017 at the institutional orthopedic wards. Written informed consents were obtained from patients or their surrogates.

Patients

All adult patients (18 to 70 years old) with body mass index (BMI) 17 to 30 kg/m² and the American Society of Anesthesiologists (ASA) physical status classification I-III scheduled for elective knee or ankle arthroscopy surgery under spinal anesthesia were eligible. The exclusion criteria were patients with contraindication for spinal anesthesia, anesthetic level after spinal block under the tenth thoracic spinal nerve (T10) or above the fourth thoracic spinal nerve (T4), tympanic membrane temperature at pre-operative holding area of less than 35.5°C or more than 37.5°C, receiving beta adrenergic blockers or alpha adrenergic blockers, otitis or other ear infection, blood pressure at pre-operative holding area more than 140 over 90 mmHg, and patient's withdrawal or refusal.

Study protocols

On pre-operative holding area arrival, patients were randomized into two groups, control and ephedrine group, using a computer-generated randomization list in a sealed envelope. Both groups received oral midazolam 7.5 mg for pre-medication 30 minutes before scheduled surgery time and received 500 ml warmed ringer acetate (41°C) for pre-loading fluid, then spinal anesthesia was performed with 3.2 ml of 0.5% hyperbaric bupivacaine. Immediately after the spinal subarachnoid bupivacaine administration, 3 ml of normal saline was intravenously given to the patients in the control group as placebo, while 9 mg of ephedrine was given to the patients in the ephedrine group. All study drugs were prepared in identical 3 ml clear solution by another anesthesiologist who did not attend the case and the anesthesiologists who attended the case were blinded to the patients' groups. After checking for anesthetic level, the surgery proceeded without sedation throughout the study period. All the patients received warmed ringer acetate (41°C) as maintenance and replacement fluid. The rate of intravenous fluid infusion during the study was adjusted based on the attending anesthesiologist's judgement. After the surgery was finished, all the patients were transferred to the post-anesthetic care unit.

Demographic data and baseline characteristics were recorded when the patients arrived at the pre-operative holding area. Tympanic membrane temperature (surrogate for body temperature, Braun ThermoScan® PRO 4000, Kaz USA, Inc., Southborough, MA, USA) and blood pressure were recorded at the pre-operative holding area, after pre-loading (before spinal block), immediately after spinal subarachnoid injection, at 2.5, 5, 7.5, and 10 minutes after injection, and at 10-minute interval thereafter until 120 minutes after injection (T2.5, T5, T7.5, ..., T120). Operating room temperature, blood loss, and amount of fluid given were recorded at end of the study periods. Total anesthesia time was recorded when the patients arrived at the post-anesthetic care unit.

During the study period, forced-air warming device was applied when the patient's temperature fell below 35°C and the event was recorded. If the patient had shivering, 25 mg of pethidine was given, and the event was recorded. If systolic blood pressure decreased to less than 90 mmHg or more than 20% from baseline, 300 ml of ringer acetate was infused, and blood pressure was re-measured five minutes thereafter. If systolic blood pressure was still lower than the aforementioned criteria, 3 mg of ephedrine was given at 2.5-minute interval with concomitant ringer acetate loading and the event was recorded as hypotension. The primary outcome was difference of tympanic membrane temperature at time points compared with before performing spinal block (after pre-loading).

Based on a previous study on effect of ephedrine on body temperature in patients under general anesthesia, the mean body temperature of patients who received ephedrine was higher than placebo by about 0.4°C (35.9°C and 35.5°C) with the standard deviation (SD) of 0.4 at 75-minute after the first evaluation[6]. The sample size needed to have sufficient power (80%) to detect this difference between two parallel groups with a 0.050 significance level based on a two-tailed independent test was 16 patients in each group. To incorporate a dropout rate of 20%, the total sample size was rounded up to 40.

Statistical analysis

Statistical analysis was performed using the PASW Statistics for Windows, version 18.0 (SPSS Inc., Chicago, Ill, USA). Continuous data were assessed for normal distribution. Parameters were represented as means ± SD unless indicated specifically. The comparisons of profile and other

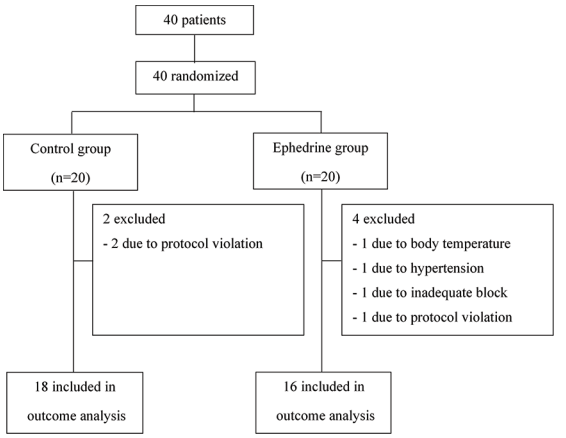

Figure 1. Flow chart.

outcomes between ephedrine and control groups were performed by independent sample t-tests, Mann-Whitney or chi-square tests where appropriate. Differences of body temperature and blood pressure from before spinal block to multiple specific time points were evaluated using two-way repeated-measures ANOVAs against the factors of group and time. A p-value of less than 0.050 was considered statistically significant.

Results

Patients

Forty patients were enrolled, and were randomized into two groups of 20 each. In the control group, two patients were excluded due to study protocol violation. In the ephedrine group, four patients were excluded from outcome analysis as one patient had body temperature at pre-operative holding area greater than 37.5°C (37.9°C), one patient had hypertension, one patient had inadequate anesthetic level (failed spinal block), and one patient due to study protocol violation (Figure 1).

Demographic data

All baseline data and characteristics were similar between the study groups. Operating room temperature, anesthesia time, and amount of fluid given were comparable between the groups. No patient had significant blood loss (more than 100 ml). Blood pressure and body temperature at pre-operative holding area were not statistically different (Table 1).

Tympanic membrane temperature

After subarachnoid bupivacaine injection, body temperature gradually declined in both groups. In the ephedrine group, body temperature exhibited biphasic pattern, early declining and late increasing, with nadir at around 50 minutes after injection. The pattern was not observed in the control group, which declined more rapidly. The difference of changes became more apparent and became statistically different overtime (Table 2). Although not statistically significant, patients in the control group had higher incidence of body temperature of less than 35% [6 of 18 (33.33%) versus 1 of 16 (6.25%), p=0.090] and shivering [6 of 18 (33.33%) versus 3 of 16 (18.75%), p=0.448) (Table 3, Figure 2).

Blood pressure

In control group, the blood pressure fell below

Table 1. Demographic and baseline data (total=34)

	Control (n=18) Mean±SD	Ephedrine (n=16) Mean±SD	p-value
Age (year)	37.28±10.24	32.75±13.07	0.267
Sex: male/female; n	13/5	11/5	>0.999
BMI ($kg.m^{-2}$)	23.89±3.32	23.47±2.73	0.692
Anesthesia level; median (IQR)	T8 (T10 to T6)	T8 (T10 to T6)	0.986
Operative room temperature (°C)	21.47±1.26	22.03±0.97	0.160
Anesthesia time (minute)	124.44±35.35	140.31±29.35	0.167
Intravenous fluid (ml); median (IQR)	1,100 (1,000 to 1,300)	1,100 (875 to 1,200)	0.330
Pre-operative body temperature (°C)	36.68±0.3	36.72±0.44	0.783
Pre-operative systolic blood pressure (mmHg)	124.89±13.8	122.56±10.97	0.593
Pre-operative diastolic blood pressure (mmHg)	73.39±10.51	75.06±10.31	0.643

BMI=body mass index; SD=standard deviation; IQR=interquartile range

Table 2. Mean body temperature (°C) at different time points

	Control (n=18); mean±SD			Ephedrine (n=16); mean±SD			p-value‡
	Mean body temperature (°C)	Mean difference from before SB	p-value†	Mean body temperature (°C)	Mean difference from before SB	p-value†	
Before SB	36.52±0.38	-	-	36.78±0.43	-	-	-
Immediate post-SB	36.48±0.44	−0.04±0.25	0.522	36.74±0.39	−0.03±0.11	0.264	0.067
T2.5	36.43±0.49	−0.09±0.24	0.134	36.65±0.41	−0.13±0.37	0.192	0.096
T5	36.35±0.46	−0.17±0.34	0.047*	36.59±0.41	−0.19±0.36	0.058	0.070
T7.5	36.21±0.34	−0.32±0.39	0.003*	36.54±0.33	−0.24±0.5	0.078	0.007*
T10	36.14±0.36	−0.38±0.38	0.001*	36.46±0.39	−0.31±0.42	0.010*	0.018*
T20	35.96±0.39	−0.57±0.33	<0.001*	36.22±0.39	−0.56±0.48	<0.001*	0.034*
T30	35.86±0.51	−0.67±0.47	<0.001*	36.13±0.41	−0.64±0.48	<0.001*	0.043*
T40	35.74±0.6	−0.78±0.58	<0.001*	35.98±0.49	−0.8±0.38	<0.001*	0.098
T50	35.73±0.57	−0.79±0.6	<0.001*	35.96±0.61	−0.82±0.5	<0.001*	0.107
T60	35.69±0.62	−0.83±0.71	<0.001*	36.04±0.56	−0.73±0.49	<0.001*	0.037*
T70	35.75±0.63	−0.77±0.79	0.001*	36.0±0.66	−0.78±0.56	<0.001*	0.083
T80	35.73±0.64	−0.79±0.78	0.001*	36.01±0.67	−0.77±0.55	<0.001*	0.079
T90	35.65±0.79	−0.87±0.89	0.001*	36.08±0.61	−0.7±0.48	<0.001*	0.035*
T100	35.58±0.77	−0.94±0.82	<0.001*	36.11±0.64	−0.66±0.51	<0.001*	0.018*
T110	35.58±0.72	−0.94±0.8	<0.001*	36.19±0.62	−0.59±0.42	<0.001*	0.009*
T120	35.47±0.77	−1.05±0.76	<0.001*	36.17±0.61	−0.61±0.46	<0.001*	0.006*

SB=spinal block; SD=standard deviation

† Compared to temperature before SB within separate groups using paired t-test; ‡ p-value indicate the result of ANOVA for repeated measures between the two groups (ephedrine vs. control; independent groups) from before SB to such time points; * Statistical significance, p<0.05

Table 3. Shivering and related outcomes

	Control (n=18) n (%)	Ephedrine (n=16) n (%)	p-value
Body temperature <35°C	6 (33.33)	1 (6.25)	0.090
Shivering	6 (33.33)	3 (18.75)	0.448
Rescue ringer acetate infusion	3 (16.67)	1 (6.25)	0.604
Hypotension	1 (5.56)	1 (6.25)	>0.999

baseline after receiving the placebo. In the ephedrine group, the blood pressure rose initially after receiving the intravenous ephedrine then fell below baseline. More patients in the control group needed rescue 300 ml ringer acetate infusion for low blood pressure [3 of 18 (16.67%) versus 1 of 16 (6.25%), p=0.604), and one patient from each group [1 of 18 (5.56%) versus 1 of 16 (6.25%), p>0.999] had hypotension (received rescue ephedrine and fluid loading) (Table 3). Overall, the blood pressure of the patients in the ephedrine group change from baseline were less prominent. The data on blood pressure is shown in Table 4 and Figure 3.

Discussion

Core temperature reduction attenuation effect of ephedrine was demonstrated in the present study. In concordance with other former studies, patients who received ephedrine had better body temperature preservation. Many former studies, varied in dosage and regimen, investigated the effect of ephedrine on body temperature. It was successfully used to treat cyclical hypothermia[7]. A study reported body temperature preserving effect of ephedrine infusion during spine surgery under general anesthesia[8]. In another study on patients with maternal hypotension during caesarean section under spinal anesthesia, the patients who received additional continuous ephedrine infusion demonstrated higher body temperature compared to placebo; however, both groups received bolus ephedrine[9]. Single bolus dose of ephedrine has also shown temperature preserving effect in patients under general anesthesia[6]. The authors decided to use the bolus dosage of 9 mg, which was within the common dosage, 5 to 10 mg, for treatment of intraoperative hypotension and comparable to the dosages used by former studies for hypotension prevention[10]. In the present study, from baseline, the

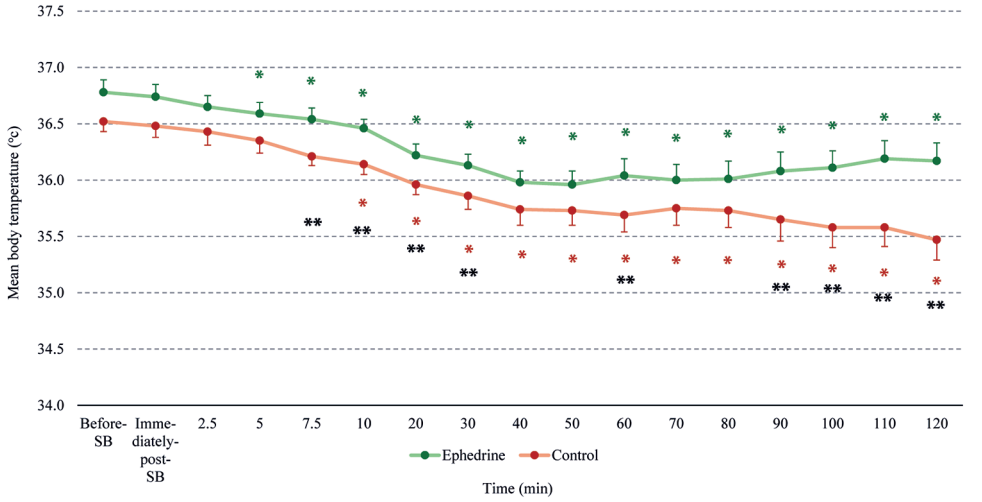

Figure 2. Body temperature changes over time.

Data are means and standard error of means, SB=spinal block,

* p<0.050, compared to temperature before spinal block within separate groups using paired t-test; ** p<0.050, statistically significant result of ANOVA for repeated measures between the two groups (ephedrine vs. control; independent groups) from before SB to such time points

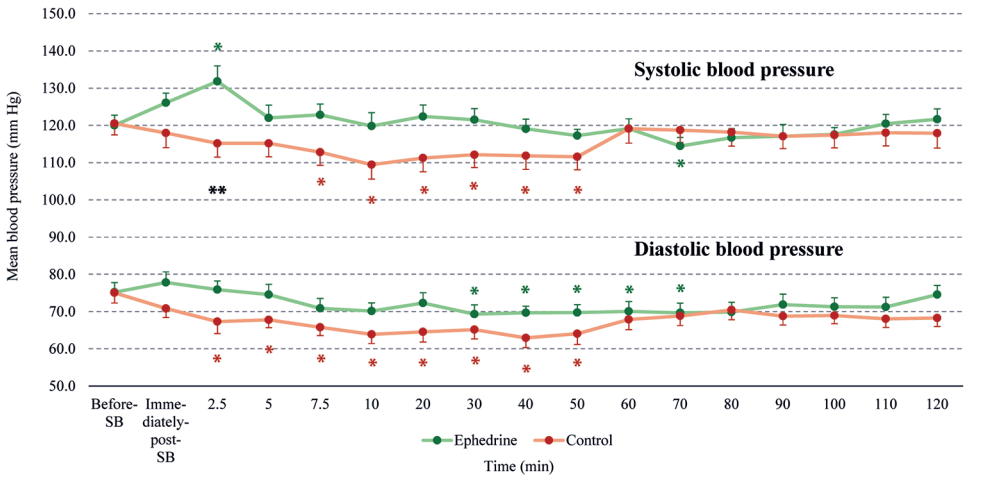

Figure 3. Blood pressure changes over time.

Data are means and standard error of means, SB=spinal block

* p<0.050, compared to temperature before spinal block within separate groups using paired t-test; ** p<0.050, statistically significant result of ANOVA for repeated measures between the two groups (ephedrine vs. control; independent groups) from before SB to such time points

gap of temperature change compared with baseline between groups was widened and became statistically significant over time. The trend continued beyond the study period. To determine the duration of this effect, a study with longer observation period is required.

Ephedrine raises blood pressure but it could also result in undesirable hypertension. Many studies investigated the efficacy of ephedrine on hypotension prophylaxis[10-12]. A former study demonstrated that ephedrine could prevent hypotension in patients that underwent cesarean section under spinal anesthesia, but the higher doses were associated with higher incidence of hypertension[12]. In the present study, the effect of ephedrine, in relatively smaller doses, was counteracted by vasodilatation from the spinal anesthesia. Therefore, the net effect on blood pressure seen in the ephedrine group was only subtle and no serious hypertensive event occurred.

Although, hypothermia has various well-established detrimental effects on patient outcome,

Table 4. Systolic and diastolic blood pressure (mmHg) at different time points

	Control (n=18); mean±SD			Ephedrine (n=16); mean±SD			p-value‡
	Mean blood pressure (mmHg)	Mean difference from before SB	p-value†	Mean blood pressure (mmHg)	Mean difference from before SB	p-value†	
Systolic blood pressure							
Before SB	120.5±12.95	-	-	120.0±10.39	-	-	-
Immediate post-SB	117.94±16.64	–2.56±12.04	0.380	126.06±16.62	6.06±14.31	0.111	0.394
T2.5	115.17±15.76	–5.33±15.79	0.170	131.81±13.61	11.81±13.67	0.004*	0.043*
T5	115.17±15.19	–5.33±15.26	0.156	122.0±11.63	2.0±15.38	0.610	0.373
T7.5	112.78±15.0	–7.72±13.21	0.024*	122.81±14.45	2.81±18.18	0.545	0.208
T10	109.44±16.35	–11.06±14.85	0.006*	119.81±12.3	–0.19±18.21	0.968	0.177
T20	111.22±15.56	–9.28±18.07	0.044*	122.38±12.0	2.38±12.51	0.459	0.142
T30	112.11±14.51	–8.39±16.54	0.046*	121.5±10.48	1.5±11.25	0.602	0.206
T40	111.83±15.45	–8.67±16.17	0.036*	119.06±6.78	–0.94±11.41	0.747	0.320
T50	111.56±14.8	–8.94±15.19	0.023*	117.25±10.58	–2.75±13.85	0.439	0.458
T60	119.11±16.5	–1.39±17.61	0.742	119.13±9.18	–0.88±11.38	0.763	0.946
T70	118.72±14.02	–1.78±15.65	0.636	114.44±9.63	–5.56±9.75	0.038*	0.492
T80	118.17±15.82	–2.33±15.76	0.538	116.69±12.74	–3.31±12.5	0.306	0.797
T90	117.06±14.03	–3.44±12.09	0.243	117.06±7.3	–2.94±11.55	0.325	0.943
T100	117.39±14.46	–3.11±13.12	0.329	117.56±9.9	–2.44±14.99	0.525	0.962
T110	118.0±14.94	–2.5±13.93	0.457	120.44±11.3	0.44±14.09	0.903	0.790
T120	117.89±16.9	–2.61±14.58	0.458	121.63±14.8	1.63±15.65	0.684	0.693
Diastolic blood pressure							
Before SB	75.06±11.72	-	-	75.19±11.49	-	-	-
Immediate post-SB	70.83±10.12	–4.22±9.01	0.063	77.81±9.45	2.63±8.32	0.226	0.301
T2.5	67.33±13.88	–7.72±14.49	0.037*	75.88±11.07	0.69±8.62	0.754	0.239
T5	67.78±9.0	–7.28±12.97	0.029*	74.56±10.51	–0.63±11.42	0.830	0.261
T7.5	65.78±9.37	–9.28±13.52	0.010*	70.88±8.74	–4.31±10.98	0.137	0.371
T10	63.89±10.42	–11.17±13.12	0.002*	70.13±10.99	–5.06±9.71	0.054	0.338
T20	64.56±11.51	–10.5±14.54	0.007*	72.31±10.03	–2.88±11.27	0.324	0.217
T30	65.17±10.78	–9.89±13.72	0.007*	69.31±7.1	–5.88±10.92	0.048*	0.466
T40	62.94±10.97	–12.11±15.05	0.003*	69.69±8.38	–5.5±9.69	0.038*	0.256
T50	64.06±12.19	–11.0±15.95	0.009*	69.75±10.46	–5.44±9.39	0.035*	0.374
T60	67.89±11.51	–7.17±16.21	0.078	70.06±10.4	–5.13±8.86	0.035*	0.717
T70	68.83±10.95	–6.22±15.37	0.104	69.69±10.43	–5.5±8.59	0.022*	0.877
T80	70.44±11.12	–4.61±16.08	0.241	69.88±11.17	–5.31±9.99	0.050	0.945
T90	68.78±10.27	–6.28±15.24	0.099	71.88±9.6	–3.31±10.63	0.232	0.586
T100	68.94±9.31	–6.11±13.39	0.070	71.31±10.36	–3.88±11.47	0.197	0.680
T110	68.06±9.7	–7.0±13.9	0.048*	71.25±9.81	–3.94±9.98	0.135	0.587
T120	68.28±9.8	–6.78±13.85	0.053	74.56±9.59	–0.63±10.2	0.810	0.295

SB=spinal block; SD=standard deviation

† Compared to blood pressure level before SB within separate groups using paired t-test; ‡ p-value indicate the result of ANOVA for repeated measures between the two groups (ephedrine vs. control; independent groups) from before SB to such time points; * Statistical significance, p<0.050

its association with perioperative shivering is complicated[13-17]. While hypothermia is known as a common cause of shivering, it also occurs in normothermic patients[18,19]. The findings from the

present study were similar where nine patients [6 of 18 (33.33%) in the control group versus 3 of 16 (18.75%) in the ephedrine group p=0.448] had shivering. Their body temperature at onset of shivering varied from 34.5°C to 37.0°C. Although patients in the ephedrine group had higher mean body temperature, the incidence of shivering was not significantly different between the two groups.

Some factors should be taken for consideration as limitation of the present study. First, the surgical technique, fluid irrigation during arthroscopy, type of sterile drape, and draping technique might have affected heat loss and were not controlled. Tympanic membrane temperature measurement is simple and non-invasive but might not accurately reflect core temperature[20]. Lastly, since the difference in hemodynamic effect could not be blinded, it could give a hint to the attending physicians about the study groups.

Conclusion

For patients undergoing knee or ankle arthroscopic surgery, a single bolus 9 mg of ephedrine given intravenously just after subarachnoid injection for spinal anesthesia could preserve core temperature with subtle effect on blood pressure.

What is already known on this topic?

Bolus ephedrine attenuates core temperature reduction in patients undergoing general anesthesia. Its effect in patients under spinal anesthesia was still not well-demonstrated.

What this study adds?

Bolus ephedrine can attenuate core temperature reduction in patients undergoing spinal anesthesia for knee or ankle arthroscopic surgery.

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Conflicts of interest

The authors declare no conflict of interest.

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