Comparison of ephedrine versus phenylephrine for prevention and treatment of hypotension following subarachnoid block for elective caeserean section

Original Article

Emmanuel Ikechukwu Oparanozie, Olanrewaju Oyedepo, Israel Kolawole

Department of Anesthesia University of Ilorin Teaching Hospital, Ilorin Kwara State, Nigeria

ABSTRACT

Background: Hypotension during subarachnoid block for caesarean section is common and can be harmful to both mother and the foetus. Treatment of such hypotension involves the use of intravenous fluids and vasopressors. Ephedrine has commonly been regarded as a vasopressor of choice in obstetrics but this traditional teaching has been challenged recently by authors and currently some authors have recommended phenylephrine as the vasopressor of choice in pregnancy.

Objective: To compare the incidence of hypotension in pregnant women who received ephedrine or phenylephrine for prevention and treatment of maternal hypotension following subarachnoid block for caesarean section.

Methods: This was a prospective randomized double-blind trial of 62 pregnant women who underwent elective caesarean section under subarachnoid block. Patients were divided into 2 groups (n = 31 each), Group E and Group P. Group E received ephedrine infusion while group P received phenylephrine infusion. Vital signs (blood pressure, heart rate and peripheral arterial oxygen saturation) were recorded throughout the surgery.

Results: There was no difference in the overall maternal haemodynamic profile in both groups and the neonatal outcomes were similar. The incidence of hypotension in the ephedrine and phenylephrine groups were 6.7 % and 3.2 % respectively with an overall incidence of 8.1 %.

Conclusion: Although phenylephrine showed more stable maternal haemodynamic profile around the baseline, both ephedrine and phenylephrine were equally effective and thus good options in the management of hypotension in pregnant women during caesarean section under subarachnoid block.

Key Words: Caesarean section, ephedrine, hypotension. phenylephrine.

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Corresponding Author: Emmanuel Ikechukwu Oparanozie, MSC, Department of Anaesthesia University of Ilorin Teaching Hospital, Ilorin Kwara State, Nigeria, **Tel.:** +2348065148114, **E-mail:** opansky2004@yahoo.com

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INTRODUCTION

Caesarean sections have increasingly been done under subarachnoid block^[1] because of its numerous advantages. These include, a short learning curve among anaesthesia residents, good patient compliance, rapid onset, dense motor and sensory block, immediate postoperative analgesia and avoidance of the complications of general anesthesia^[2]. However, despite all these numerous advantages, spinal anaesthesia is not without complications. Maternal hypotension is said to be one of the commonest complication which can occur in up to 80 % of pregnant patients^[3]. Maternal hypotension can lead to maternal low perfusion pressure, manifested as nausea-vomiting, dizziness, loss of consciousness and utero-placental hypo perfusion with foetal hypoxia and acidosis^[3]. Prevention and prompt treatment of this hypotension is important to ensure good foeto-maternal outcomes. Methods that have been employed to prevent or treat spinal anaesthesia-induced hypotension in obstetrics include Left lateral uterine displacement, intravenous

(i.v.) colloid or crystalloid pre-loading and co-loading as well as the use of vasopressors^[4]. This has proved insufficient^[5, 6] hence a multimodal approach centred on prompt use of vasopressors as recommended by NICE and ASA remains the best option^[4, 7, 8]. Currently, the two most commonly used vasopressors are ephedrine and phenylephrine^[9]. Traditionally, ephedrine has been the preferred choice for the management of maternal hypotension during spinal anaesthesia for elective caesarean delivery in healthy, non labouring women^[4], but this has been challenged byother authors^[10, 11]. Ephedrine has been associated with tachyarrhytmias, exhibiting tachyphylaxis and has been postulated to adversely affect foetal metabolism, unlike phenylephrine. Some authors recommended phenylephrine^[12, 13], while others found no differences between the two^[8, 14]. However most of these studies had taken a reactive approach to prevention of spinal hypotension. Odagme et al.,[15] employed a prophylactic approach by running background infusions following spinal and although they found no difference in the incidence of hypotension between the groups,

the overall incidence of hypotension in the study was a little high. This study employed a similar but modified prophylactic approach, as protocols that have adopted a prophylactic rather than reactive approach to treatment has been shown to yield better outcomes^[4]. It was believed that this will add to the body of knowledge on this subject.

This randomized double-blind study compared the effects of prophylactic bolus and infusion administration of ephedrine and phenylephrine on the control of maternal haemodynamic parameters during subarachnoid block for caesarean section.

METHODS AND MATERIALS

The study was carried out at the University of Ilorin Teaching Hospital Ilorin following ethical approval from the institution's ethical board and consent from enrolled patients. The study adhered to full ethical standards of the Helsinki declaration and was supervised by the institutional ethical review board. Sixty-two (62) consenting pregnant women scheduled for elective caesarean section under subarachnoid block were involved in the randomized double-blind trial. Consenting patients were allotted by a research assistant into two groups, E (ephedrine group) and P (phenylephrine group) on the morning of surgery, using simple random sampling technique. Both the patient and the researcher were blinded to the group the patient fell into as only the research assistant was aware of this. The research assistant prepared the study drugs. The study drugs were 5 mg/ml and 50 µg/ml of ephedrine and phenylephrine bolus injections for groups E and P respectively, each contained in identical 5 ml syringe. The research assistant also set up 20 ml infusions of ephedrine and phenylephrine each in a syringe pump (Terfusion syringe pump TE-331. Terumo corporation 44-1, 2-Chome, Hatagaya, Shibuya-Ku, Tokyo 151-0072.) containing 4mg/ml of ephedrine and 50 µg/ml of phenylephrine which was administered to groups E and P respectively. This was labeled as infusion drugs and the researcher was blinded to the content. The infusion rate was chosen based on an already determined equipotent infusion rate of both drugs by Saravan et al.,[16] (80:1). The study drugs were handed over to the researcher who administered them. All consenting pregnant women above 18 years scheduled for elective caesarean section at term under subarachnoid block were included while exclusion criteria included patient's refusal, contraindications to subarachnoid block, high risk pregnancies (multiple gestations, intrauterine growth retardation, preeclampsia, eclampsia or pregnancy induced hypertension, maternal cardiovascular or pulmonary diseases, ante partum haemorrhage),and ASA III and above patients. Data collection lasted 6 months.

Patients received appropriate pre anaesthestic review and care and informed and written consent obtained. Routine fasting guidelines and acid aspiration prophylaxis were instituted. On arrival at the operating suite, a preanaesthetic check was carried out to ensure optimum functioning of all anaesthetic work station. Patient was positioned on the operating table in left lateral position and connected to a multiparameter patient monitor (DASH 4000, GE Medical systems information technologies Inc. 8200W. Tower Ave Milwaukee, Wisconsin USA). Baseline values for systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), pulse rate (PR), peripheral arterial oxygen saturation (SpO₂), temperature and electrocardiogram (ECG) were obtained and documented.Two intravenous accesses were secured with a size 16 G cannula (fluid IV line) and size 18 G cannula (test drug line).

Before performing spinal anaesthesia, all patients received about 15 mls/kg normal saline from fluid IV line as fast as possible using a pressure infusor. Thereafter, subarachnoid block was performed in sitting position after routine cleaning and draping using theL3/L4 or L4/L5 interspace by the researcherwith the aid of a 25 - 26 G Quincke spinal needle.Hyperbaric bupivacaine 12.5 mg and 25 µg fentanyl was injected. Thereafter, patient was repositioned supine with a wedge under the right hip and head elevated with a pillow. The block height was assessed by response to cold sensation using alcohol swab and block height of T6 was considered appropriate. Immediately after performing the block, both groups received 1 ml bolus of study drug corresponding to 5mg ephedrine bolus for the ephedrine group and 50 µg phenylephrine bolus for the phenylephrine group administered by the researcher who also commenced the infusion drugs at 1 ml/min corresponding to 4 mg/min ephedrine and 50 µg/min phenylephrine for groups E and P respectively using syringe pumps. The researcher was in charge of data collection and handed over the proforma to the research assistant to indicate the group at the end of the study. A stop watch was used to measure the following time intervals, from spinal injection to positioning of the patient in supine position, from spinal injection to skin incision, from spinal injection to delivery of the baby, from skin incision to delivery and time from uterine incision to delivery of baby. Vital signs were recorded every 2 minutes for the first 20 minutes following the block and subsequently measured at 5 minutes interval till end of surgery. In cases of hypotension (defined as a decrease in systolic arterial pressure > 20 % of baseline) necessitating breakthrough vasopressor while the infusion was ongoing, the researcher administered 1ml bolus of the study drug earlier prepared by the research assistant. Once the blood pressure remained stable around the baseline for more than 15 minutes after establishment of the block or following development of reactive hypertension, vasopressor infusion was discontinued and total dose of vasopressor used was calculated. Reactive hypertension was defined

as blood pressure 20 % higher than the baseline level following the use of vasopressors. Heart rate below 60 beats per minute was defined as bradycardia. Tachycardia was defined as a heart rate which was higher than 100 beats in a patient whose baseline heart rate was less than 100. Apgar scores of the neonate were noted at first and fifth minute. Five IU bolus of oxytocin was given intravenously to the mother at the delivery of the baby and 40 IU was added to 1 litre of normal saline to run slowly. Further management of the patient was continued at the discretion of the attending anaesthetist. The primary outcome measure was mean lowest SBP while secondary outcome measures included mean DBP, MAP and HR, incidence of side effects (nausea,vomiting,hypotension, shivering, reactive hypertension) and Apgar scores at 1st and 5th minute.

DATA ANALYSIS

Data was analyzed using SPSS 20 IBM Corp., Armonk, NY, USA. Nominal data was presented as percentages and analyzed using Chi square test whileordinal variables were presented in median and rangeand analyzed using Mann-Whitney U-test. Continuous variables were presented in means and standard deviation and analyzed using the T-test. A *p*-value of < 0.05 was considered statistically significant.

From a previous study^[3], we determined that a sample size of 62 patients will be sufficient to detect an effect size of 10 mmHg in the mean SBP using a power of 90 % at the 5 % significance level.

RESULTS

Sixty-two patients gave consent and were recruited for the study comprising thirty-one patients in each group. All but one patient in the ephedrine group completed the study. The dropped outpatient had 3 previous caesarean section scars with extensive intra-abdominal adhesions which led to a significant intraoperative blood loss that required transfusion of 3 units of blood even before delivery of the baby. There was no significant difference in the demographic data between the two groups and these are summarized in Table I. The indications for caesarean section in both groups were similar as shown in Table II.

Twenty-eight (28) patients representing 93.3 % of the patients in group E and thirty (30) patients representing 96.8 % in group P respectively had their surgeries done by senior registrars. The rest were done by consultants. Details of the anaesthesia and delivery times in both groups are summarized in table III.The mean baseline systolic blood pressure was 123.67 ± 10.6 mmHg and 118.27 ± 12.57 mmHg for groups E and P respectively

(p value = 0.460). In both groups, there was an initial gradual decline in systolic blood pressure relative to baseline, the values thereafter plateaued and both groups were comparable. The trend of the systolic blood pressure in both groups is displayed in Figure 1. There was no difference in the mean diastolic blood pressure (mmHg) at baseline as shown in Figure 2 between groups E and P, 72.39 ± 6.00 and 71.39 ± 9.96 respectively (p value = 0.237). The lowest and highest values of diastolic blood pressure values during the study period was seen in the ephedrine group while the phenylephrine group had lesser variation from baseline values. The baseline mean arterial blood pressure (mmHg) for groupsEandPwere 84.11±5.70and82.61±8.11respectively (p value = 0.657). There was an initial gradual reduction in MAP values followed by a peak. The patients in the ephedrine group had more variations around the baseline as opposed to patients in the phenylephrine group who had more stable values. The general trend of the MAP is shown in Figure 3. The baseline mean pulse rate in both groups E and P were 90.44 \pm 13.32 and 88.44 \pm 10.55 respectively (p value = 0.639). From the 8th minute, patients in the phenylephrine group showed a significant reduction (p value < 0.05) in pulse rate which continued till the end of the study period. The details and trends of the heart rate in both groupsare shown in Figure 4. Five patients in total had hypotension giving an overall incidence of hypotension of 8.1 %. This comprised three patients in the ephedrine group (10 %) and two patients in the phenylephrine group (6.5%). None of the patients in either group had nausea or vomiting. One patient in the ephedrine group (3.3 %) had post spinal shivering. The number and percentages of the side effects for each group is shown in Table IV. The average total infused volume (ml) of the study drug for groups E and P was 7.1 \pm 1.2 and 8.2 \pm 0.4 respectively while the mean total study drug administered was 388.82 ± 26.78 and 413.85 ± 29.64 of phenylephrine equivalent for groups E and P respectively. The details of the total infused study drug volume, total study drug administered, estimated blood loss intraoperatively, total intraoperative fluid therapy and number of rescue bolus vasopressors are captured in Table V. There was no difference in the neonatal outcomes as shown in Table VI.

Table I: Maternal Demographic Data:

Variables	Group E (n = 30)	Group P (n = 31)	P value
Age (years)	31.2 ± 4.4	32.6 ± 3.82	0.249
Weight (kg)	83.1 ± 4.3	81.2 ± 6.5	0.325
Height (m)	1.65 ± 0.40	1.65 ± 0.36	0.605
Gestational age (weeks)	38.3 ± 1.4	38.7 ± 1.3	0.515
*Parity	3 (0 - 5)	3 (0 - 5)	

Mean \pm SD. * in median (range).

Indication	Group E	Group P	P Value
\geq 2 previous scars	22 (73.4)	21 (67.7)	0.41
Primigravida + breech	5 (16.7)	3 (9.7)	0.23
Post dates	1 (3.3)	3 (9.7)	0.12
Previous scar + short interpregnancy interval	1 (3.3)	3 (9.7)	0.18
Bad Obstetric History	1 (3.3)	1 (3.2)	0.19
Total	30 (100)	31 (100)	

Table III: Anaesthesia and Delivery Times:

(Mean \pm SD).

Interval (seconds)	Group E (n = 30)	Group P (n = 31)	P value
Spinal injection to supine position	4.87 ± 0.52	4.81 ± 0.44	0.798
Spinal injection to skin incision	481.95 ± 68.42	476.35 ± 71.80	0.223
Spinal injection to delivery	816.49 ± 84.87	770.55 ± 81.67	0.144
Skin incision to delivery	335.57 ± 88.13	337.94 ± 89.77	0.225
Uterine incision to delivery	39.96 ± 5.52	36.47 ± 5.61	0.404

Number (percentage).

Table IV: Incidence of side effects between the two groups:

Variable	Group E (n = 30)	Group P (n = 31)	P value
Hypotension	2 (6.9)	1 (3.3)	0.65
Nausea	0 (0)	0 (0)	
Vomiting	0 (0)	0 (0)	
Shivering	1 (3.4)	0 (0)	0.41
Tachycardia	4 (13.8)	0 (0)	0.005
Bradycardia	0 (0)	1 (3.3)	0.41
Reactive Hypertension	1 (3.4)	0 (0)	0.41

Number (percentage).

 Table V: Details of HaemodynamicManagement:

		Group E(n = 30)	Group $P(n = 31)$	P value
Total study drug infusion volume (ml)		7.1 ± 1.2	8.2 ± 0.4	0.232
Total study drug administered (phenylephrine equivalen	t) ^a	388.82 ± 26.78	413.85 ± 29.64	0.723
Estimated blood loss(ml)		833.33 ± 157.18	816.67 ± 115.04	0.562
Total intraoperative fluid administered(ml)		2922.22 ± 239.01	2900.00 ± 157.18	0.771
Bolus vasopressor for treatment of hypotension, n (%)	Total (n = 61)			
0	56 (91.8)	27 (90.0)	29 (93.5)	0.74
1	3 (4.9)	1 (3.3)	2 (6.5)	0.35
2	1 (1.6)	1 (3.3)	0 (0)	0.42
≥3	1 (1.6)	1 (3.3)	0 (0)	0.42

Data are Mean \pm SD or Number (percentage). aAccording to equipotent infusion rate described by Savaran *et al.*,^[16].

Table VI: Neonatal outcomes:

Variable	Group E (n = 30)	Group P (n = 31)	P value
Birth Weight(kg)	3.27 ± 0.14	3.33 ± 0.15	0.264
*One minute Apgar	7 (6 - 8)	7 (7 - 8)	0.764
*5 minutes Apgar	9 (8 - 10)	9 (8 - 10)	0.665

Mean \pm SD,* median(range).

5

Figure 2: Trends in diastolic blood pressure (mmHg) in the two groups.



Figure 1: Trends in systolic blood pressure (mmHg) in the two groups.





Figure 3: Trends in mean arterial pressure (mmHg) in both groups.



Figure 4: Trends in pulse rates in both groups.

6

DISCUSSION

The study showed that prophylactic administration of vasopressors (ephedrine and phenylephrine) was associated with fewer incidences and severity of maternal hypotension following subarachnoid block. Parturients from both groups had good haemodynamic control with phenylephrine group being slightly more stable.

Of the sixty-one (61) patients who completed the study and were analysed, only 5 (8.1 %) developed hypotension. Odagme et al.,^[15] reported an incidence of 8.5 % in their study and is comparable to this index study. The slightly but insignificant higher incidence of hypotension in their study could be because of two reasons; first, they employed combined spinal epidural as their anaesthetic technique. While this is advantageous in offering excellent postoperative analgesia, distention of the subarachnoid space which occurs in combined spinal epidural can lead to higher dermatomal spread of the local anaesthetic agent and invariably lead to hypotension. This is of particular importance in pregnant women who already have contracted epidural space as the contracted space predisposes them to higher dermatomal spread and increased likelihood of hypotension^[17]. The higher dermatomal spreadof SAB reported in Odagme et al's.,[15] study could also have contributed to the slight but insignificant higher incidence of hypotension in their study. From their study, the average dermatome was T5 while in the index study, a dermatomal level of T6 was employed. Higher dermatomal spread of local anaesthetic agent have been associated with higher incidence of hypotension^[17]. Adigun et al.,^[18] reported an incidence of hypotension of 24.2 % in their study. This is despite the fact that they defined hypotension in their study as \geq 30 % decrease from baseline which means it could have been higher if the definition was ≥ 20 % as used in the index study. The incidence of hypotension derived by different studies depends on the definition employed by such study. Klohr et al.,^[19] reviewed 63 different studies of hypotension following caesarean section with spinal or combined spinal epidural over a 10 year period and found 15 different definitions of hypotension. The most common definitions of hypotension used in research studies were either '< 80 % baseline' or '< 100 mmHg. Hypotension defined as < 80 % baseline was the definition used in this index study. The reason for the higher incidence of hypotension in Adigun et al's.,^[18] study could be because they did not administer vasopressor prophylactically after subarachnoid block and only did so after development of hypotension. Kinsella et al.,^[4] had argued that study protocols aimed at preventing hypotension rather than treating it had better outcomes when compared to protocols that treated after it had developed.

Desalu and Kushimo $^{\left[20\right] }$ reported an incidence of hypotension of 40 % among patients who received

ephedrine infusion and 70 % in patients who received pre-hydration alone. The average dermatomal level of the spread in their study was T4 and this could have contributed to the higher incidence of hypotension. The low incidence of hypotension (8.1 %) in the index study compared to Odagme et al.,[15] (8.5 %), Adigun et al.,^[18] (24.2 %) and Desalu and Kushimo^[20] (40 %) could be because patients were not only preloaded with normal saline, but in addition had a bolus of vasopressor administered before the background infusion could deliver enough volume to the circulation, had a background infusion of vasopressor and the researcher employed left uterine displacement. Although co-loading is now being advocated in conjunction with vasopressor^[17], preloading had been the main stay and is currently still being practiced. Preloading was also employed in this study as well as by Adigun et al.,^[18], Odagme et al.,^[15] and Desalu and Kushimo^[20]. By increasing circulating volume, preloading helps to increase preload and help combat hypotension. Notwithstanding this, preloading does not always eliminate hypotension but rather does reduce its incidence and severity which was why Sklebar et al.^[17] recommended a multimodal approach to preventing maternal hypotension, involving combination of preloading/co-loading, uterine displacement, use of small doses of local anaesthetics combined with opioid as well as early use of vasopressors. All of these were employed in the index study. The infusion rate of ephedrine and phenylephrine employed in this study were equipotent as described by Saravana et al.,[16] with both agents maintaining blood pressure although this study showed that phenylephrine maintained systolic, diastolic and mean arterial blood pressure slightly better around baseline values compared with ephedrine. This is in agreement with the findings of Adigun et al.,[18] and Odagme et al.,^[15] In this study, (3.3 %) patients in the ephedrine group and none in the phenylephrine group developed reactive hypertension. Odagme et al.,[15] on the other hand, reported an incidence of (10 %) and (3.4 %) patients in phenylephrine and ephedrine groups respectively. This could be because Odagme et al.,^[15] used 80 µg/minute infusion rate as compared to 50 µg/minute employed in the index study.

In terms of pulse rate, patients in the ephedrine group showed a slight increase in pulse rate whereas patients in the phenylephrine group showed a significant reduction in pulse rate over time. This agrees with the findings of Odagme *et al.*,^[15], Adigun *et al.*,^[18], Ngan *et al.*,^[14]. The incidence of bradycardia and tachycardia varies between studies due to definition of bradycardia and tachycardia employed by different authors. It is therefore possible that if the heart rate were defined in terms of percentage increase or decrease for tachycardia and bradycardia, the incidence noted may have differed. Notwithstanding, from the 8th minute of the study, the heart rate difference between the two groups in this study became very obvious with statistically significant difference (p-value < 0.05) till the end of the study. This was the same trend reported by Adigun *et al.*^[18] and this may be reflective of the fact that at such time, the peak onset of action of the vasopressors had been reached and as such their systemic effect was becoming obvious. The one case of bradycardia in the phenylephrine group in this study did not occur with hypotension. This is important because bradycardia occurring with hypotension following subarachnoid block could be an early warning, signaling an impending danger as it indicates possible high spinal, which if not urgently and adequately managed can lead to cardiac arrest. Oxytocin causes tachycardia and hypotension especially when given as a bolus in doses greater than 10 IUwhen compared with slow titration as an infusion^[21]. Hence this study employed the use of 5 IU of oxytocin bolus which is the dose recommended by the Confidential Enquiries into Maternal Death (CEMD) as the optimum dose to prevent haemodynamic compromise while achieving good uterine contraction^[21].

None of the patients in this study had nausea or vomiting while Odagme et al.,^[15] and Adigun et al.,^[18] reported an overall incidence of 1.7 % and 11.3 % respectively, while in the study by Desalu and Kushimo^[20], 39.4 % of all hypotensive patients had nausea and vomiting. The incidence of nausea and vomiting recorded in these studies may not be unconnected with the higher incidences of maternal hypotension they recorded (8.5% for Odagme et al., [15], 24.2% for Adigun et al., [18] and 40 - 70% for Desalu and Kushimo^[20]). Maternal hypotension during subarachnoid block have been associated with increased incidence of nausea and vomiting^[9, 11, 22 - 23]. This is believed to be caused by hypoperfusion of the chemoreceptor trigger zone following hypotension, along with release of emetogenic substances like serotonin due to gut hypo perfusion^[24]. Thus, prevention and early treatment of hypotension will decrease the incidence and severity of nausea and vomiting. Bowel manipulation as well as intravenous opioid use are other causes of nausea and vomiting.

None of the patients in this study developed post spinal shivering. This could be because the fluids were warmed before administration. This is similar to the findings of Adigun *et al.*,^[18]. Although the exact mechanism of post spinal shivering remains unclear^[25], various postulatory mechanisms have been put forward to explain it. It has been attributed to a thermoregulatory response to hypothermia that causes temperature-induced changes of neurons in the mesencephalic reticular formation^[26]. Apgar scores is a method of assessing foetal outcome. The index study found that there was no significant difference between the first and fifth minutes Apgar scores in the

neonates from both groups. This agrees with the findings of Odagme *et al.*,^[15], Adigun *et al.*,^[18], Higgins *et al.*,^[27], Vakili *et al.*,^[28] and Prakash *et al.*,^[29].

CONCLUSION

Although phenylephrine showed more stable maternal haemodynamic profile around the baseline, both ephedrine and phenylephrine were equally effective and thus good options in management of hypotension in pregnant women during caesarean section under subarachnoid block and both are recommended for use in the management of hypotension in caesarean section.

IMPLICATION FOR PRACTICE

Both ephedrine and phenylephrine are effective in management of maternal hypotension in caesarean section. Although phenylephrine is relatively more expensive in our environment, where wide fluctuations in haemodynamic parameters are highly undesirable, phenylephrine may be a better option while in cases of low baseline heart rate, ephedrine may be a better option.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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