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Phenylephrine versus cafedrine/theodrenaline (Akrinor) for the treatment of spinal anaesthesia-induced maternal hypotension during caesarean section: a retrospective single-centre cohort study

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ABSTRACT

Objective The main objective of this study was to assess the impact of phenylephrine and cafedrine/theodrenaline on the mother and newborn after spinal anaesthesia for caesarean section.

Setting University teaching hospital.

Design A single-centre retrospective data cohort study.

Patients All obstetric patients who were scheduled for caesarean section in a 2-year period.

Interventions Administration of either intravenous phenylephrine prophylactically or cafedrine/theodrenaline (Akrinor) reactively to maintain blood pressure after spinal anaesthesia.

Main outcome measure Maternal hypotension, heart rate during caesarean section and after admission to IMC, fetal arterial cord pH and base excess levels, maternal volume resuscitation and the use of rescue medication.

Results 852 data sets could be included: n=440 Akrinor, n=412 in the phenylephrine cohort. During caesarean section blood pressure was slightly higher in the phenylephrine group compared with the Akrinor group, while hypotension <100 mm Hg systolic blood pressure (SBP) occurred significantly more often during arrival at the IMC after surgery when phenylephrine was used. Heart rate was lower and rescue medication was significantly more frequently given in the phenylephrine cohort. Irrespective of the medication used, women with baseline levels of <120 mm Hg SBP had a high risk to develop hypotension <100 mm Hg after spinal anaesthesia for caesarean section. While there was no statistical difference in mean umbilical arterial pH levels, the incidence of acidosis, defined as pH <7.2, was significantly higher with phenylephrine.

Conclusion Phenylephrine was not superior to Akrinor to treat spinal anaesthesia-induced maternal hypotension during caesarean section.

Trial registration number DRKS00025795.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Data are derived from a single centre and the study design is retrospective.
⇒ Data cover a 2-year period but are collected from handwritten protocols.
⇒ The major strength of this study is the largest sample size comparing cafedrine/theodrenaline (Akrinor) with phenylephrine to treat maternal hypotension during caesarean section.
⇒ Haemodynamic data on intermediate care were also included.

INTRODUCTION

The caesarean section (CS) rate averages around 21.1% worldwide, ranging from 5% to 42.8%.[1] Over the last decades its frequency increased continuously in low, middle and high-income countries.[1] Fifty per cent of cases are primary CS and spinal anaesthesia (SPA) is considered to be the gold standard.[2 3] SPA-induced maternal hypotension (SMH) is the most common adverse effect during CS (described in up to 75%[4]). The pathophysiological cause of SMH is identified as: (a) sympathetic block, (b) arteriolar vasodilatation, (c) decreased systemic vascular resistance, and (d) reduction of venous vascular tone.[5 6] SMH reduces subjective well-being of the mother by inducing vomiting, nausea and dizziness and serves as a relevant clinical outcome parameter.[4] Furthermore, SMH can decrease uteroplacental blood flow which results in fetal acidosis, lower APGAR scores and neurobehavioural changes at days 4–7 of life.[7]

The use of vasopressors is one of the pillars of the therapy of SMH.[5] Ephedrine and phenylephrine (P) are the internationally most widely used vasopressors to treat SMH and are recommended by international

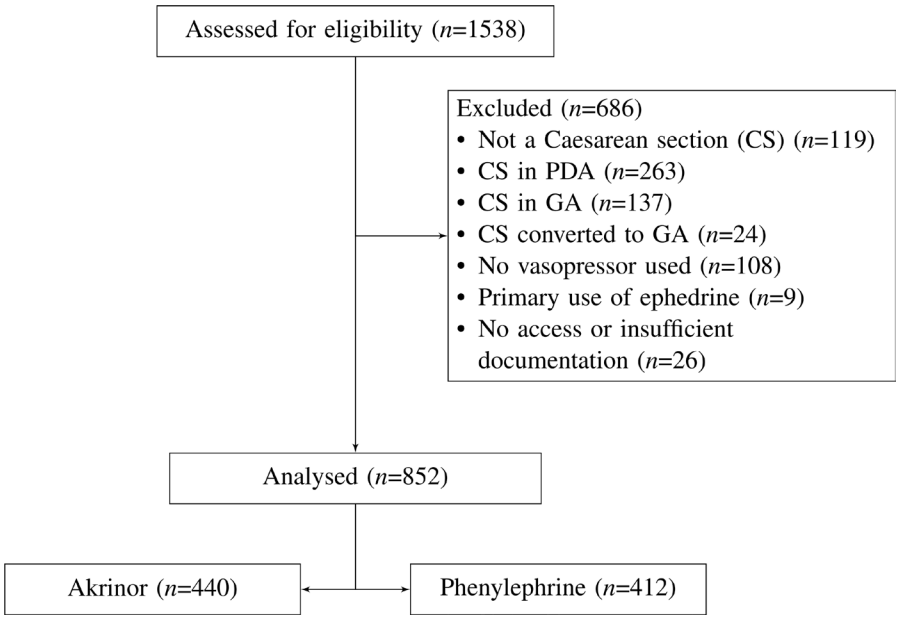

Figure 1 Flow chart showing included and excluded data sets. GA, general anaesthesia; PDA, peridural anaesthesia.

guidelines.[5] Interestingly, in European countries the choice and method of vasopressor administration during CS differ widely.[8] A German survey found that Akrinor (AK; a 20:1 mixture of cafedrine hydrochloride 200 mg and theodrenaline hydrochloride 10 mg) was the most used vasoactive substance to treat SPA-induced hypotension (86.2%) in the labour room and obstetric OR.[9] AK is usually given as an intravenous bolus and has β_1 and α_1 adrenoreceptor activity (for details see review[10]). Therefore, AK (a) increases cardiac output (CO) with stable maternal heart rate and (b) vascular resistance. Despite the routine use of AK, there are nearly no data for the treatment of SMH with AK available. To date, only one retrospective study exists that compared AK and P for the treatment of hypotension during CS. This study did not show superiority of one substance.[11] The authors summarised that the results may be confounded by differences in fluid management. The only prospective study to date is the HYPOTENS study that compared AK with ephedrine for the treatment of hypotension during CS. Blood pressure (BP) stabilisation was faster and more pronounced with AK.

To generate more scientific insight for the routine use of AK, we conducted this single-centre retrospective study to compare the impact of (a) AK and (b) P on mother and fetus during CS. We hypothesised that treatment of SMH in CS with bolus application of AK is as effective as a prophylactic infusion of P in stabilising maternal haemodynamics.

MATERIALS AND METHODS

This study is a single-centre cohort study which was performed at the university hospital of the University of Freiburg, Germany. We retrospectively compared a cohort of patients receiving AK as primary vasopressor for treatment of SMH under CS in the year 2014 with the cohort of women receiving P as primary vasopressor in 2016.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

Patient population

The standard operation procedure (SOP) for CS changed in the middle of the year 2015 from AK to P for maintaining BP after induction of SPA. Therefore, we included all patients who were scheduled for CS during the years 2014 (AK SOP) and 2016 (P SOP). Out of these patients, all who received SPA were included.

Definition of hypotension

Hypotension was defined as a decrease in mean arterial pressure (MAP) of ≤20% of the baseline value (t_0) and/or the occurrence of systolic blood pressure (SBP) less than 100 mm Hg.

Study medication and procedure

Study medications were (1) AK (cafedrine hydrochloride 200 mg, theodrenaline hydrochloride 10 mg, per 2 mL solution for injection; ratiopharm, Ulm, Germany) as primary vasopressor in the year 2014 and (2) P 10 mg/mL (Sintetica; Sintetica, Münster, Germany) as primary vasopressor in 2016.

Management of study medication

AK was given as an intravenous bolus injection usually diluted in 8 mL NaCl 0.9% or undiluted in case of emergency. All application dosages of AK were adjusted to the diluted version (cafedrine hydrochloride 20 mg/mL and theodrenaline hydrochloride 1 mg/mL) for calculation. According to the standard operating procedure, AK

Table 1 Maternal and neonatal characteristics

	n=852	Akrinor (AK) n=440	Phenylephrine (P) n=412	P value
Maternal characteristics				
Age (years)	852	32.4±5.3	32.0±5.7	0.314
ASA classification*	852	2.1±0.2	2.1±0.2	0.950
ASA II		419 (95.2)	392 (95.1)	0.956
ASA III		21 (4.8)	19 (4.6)	0.912
ASA IV		0 (0)	1 (0.2)	0.484
Pre-eclampsia	852	37 (8.4)	23 (5.6)	0.107
Cardiovascular history	852	19 (4.3)	11 (2.7)	0.192
BMI (kg/m^2)	850	29.5±5.8	29.1±5.8	0.328
Gravida	852	2.2±1.2	2.3±1.3	0.090
Para	852	0.9±1.0	1.0±1.1	0.057
Neonatal characteristics				
Gestational age (days)	847	262.4±21.0	261.9±21.8	0.969
Number of children	852	1.1±0.3	1.1±0.3	0.508
Singleton pregnancy		397 (90.2)	366 (88.8)	
Twin pregnancy		42 (9.5)	45 (10.9)	
Triplet pregnancy		1 (0.2)	1 (0.2)	
Multiple pregnancy	852	43 (9.8)	46 (11.2)	0.507
Birth size (cm)	842	49.6±4.7	49.5±5.0	0.621
Birth weight (g)	850	2951±787	2952±829	0.556
Head circumference (cm)	840	33.8±2.8	33.8±2.9	0.332

Mean±SD, n (%), n=number of cases, p value test on difference between AK and P.
*ASA classification I was corrected to II as recommended by ASA for pregnant women.
ASA, American Society of Anesthesiologists; BMI, body mass index.

should be infused if symptomatic hypotension occurred (dizziness, nausea, vomiting) or SBP decreased below 100 mm Hg. Timing and dose of AK was decided by the attending anaesthesiologist.

P 10 mg was diluted in 49 mL NaCl 0.9% (200 µg/mL) and a continuous infusion with a syringe pump was started with 0.5 µg/kg/min after induction of SPA. The dosage of P was increased to a maximum of 1.6 µg/kg/min to maintain the desired BP. AK was used as first-line and norepinephrine as second-line rescue medication in the P group. SPA was induced with intrathecal injection of bupivacaine 9 mg hyperbar combined with sufentanil 5 µg. Coloading was mostly performed with colloids infusion before S3 guideline for volume therapy was published in 2014 (www.awmf.org). Because of the rising safety concerns and the recommendation against routine use in the Germany, in some cases colloids (6% HES 130/0.4) might be used as coloading infusion in 2014.

We defined the following time points for measuring and comparing the maternal vitals: t_0=baseline, first measurement in the OR; t_1=5 min after induction of SPA; t_2=10 min after induction of SPA; t_3=last BP measurement in the OR; t_4=first BP measurement in the IMC; t_{min}=lowest SBP recorded in the OR.

Intraoperative vital parameters and given medication were extracted from anaesthetic records while postoperative vital parameters and neonatal parameters were read from digital patient records. Mean arterial BP was calculated with $\text{MAP} = \text{DBP} + \frac{SBP-DBP}{3}$.

Trial endpoints

Decrease of 20% in mean arterial maternal BP compared with baseline (t_0) and/or SBP <100 mm Hg, fetal pH and base deficit were selected as primary endpoints. Secondary endpoints were maternal heart rate, use of rescue medication, blood loss, fluid substitution, Apgar scores and submission to PICU.

Statistical analysis

Differences between groups of metric variables were tested with two-tailed Student's t-test, if a normal distribution was given. Normality was checked with Shapiro-Wilk test and visually by quantile-quantile plots. Homogeneity of variance was checked by Levene's test. If normality was violated or the variable was ordinally scaled, the two-tailed non-parametric Mann-Whitney U test was performed. Nominal variables were tested with Pearson's χ^2 test or Fisher's exact test if the number of occurrences in a group was 5 or less. For correlation we

Table 2 Characteristics for the caesarean section

	n=852	Akrinor (AK) n=440	Phenylephrine (P) n=412	P value
Emergency	852	187 (42.5)	156 (37.9)	0.168
During on-call hours	852	151 (34.3)	110 (26.7)	0.016
Duration				
Induction of anaesthesia (min)	852	13.8±7.5	14.2±8.7	0.919
Operation (min)	852	46.0±13.9	44.6±12.2	0.148
SPA until delivery (min)	843	20.3±6.1	19.6±6.3	0.029
Volume therapy				
Crystalloids (mL)	830	1952±791	2199±887	<0.001
Colloids (mL)	852	60±170	16±94	<0.001
Colloids used	852	51 (11.6)	12 (2.9)	<0.001
Blood loss (mL)	834	512±227	520±277	0.912
Fluid balance (mL)	814	1501±765	1703±857	0.001
Rescue medication	852	20 (4.5)	90 (21.8)	<0.001
Additional vasopressor	852	2 (0.5)	59 (14.3)	<0.001
Akrinor	852		58 (14.1)	
Norepinephrine	852	2 (0.5)	1 (0.2)	1.00
Parasympatholytics	852	18 (4.1)	50 (12.1)	<0.001
Glycopyrrolate	852	2 (0.5)	1 (0.2)	1.00
Atropine	852	16 (3.6)	49 (11.9)	<0.001
Antiemetics	852	80 (18.2)	74 (18.0)	0.933
Tocolysis	852	31 (7.0)	24 (5.8)	0.469
Sulprostone	852	50 (11.4)	36 (8.7)	0.204
Postoperative length of stay (days)	852	4.4±1.3	4.3±1.5	0.062
Neonatal intensive care	852	90 (20.5)	91 (22.1)	0.242

Mean±SD, n (%), n=number of cases, p value test on difference between AK and P.
SPA, spinal anaesthesia.

used Pearson correlation coefficient. We defined α=0.05 as level of statistical significance. The analysis was performed with the statistic software R V.4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) and the tidyverse package system,[12] graphics were created using the ggplot2 package V.3.3.5 (H Wickham).

RESULTS

A total of 1538 data sheets were assessed (figure 1). Out of these, 1393 interventions were CS. SPA was the method of choice in 969 (69.6%) cases. General anaesthesia (GA) was performed for 137 women (9.8%) primarily, and 24 (1.7%) women were switched to GA secondarily. Epidural anaesthesia was used in 263 (18.9%). Ephedrine was the vasopressor of choice in 9 (0.9%) patients, and 108 (7.8%) patients did not receive any vasopressors. Eight hundred and fifty-two interventions were performed in SPA while women were treated with either AK (n=440) or P (n=412) as primary vasopressor.

Maternal and neonatal characteristics

Maternal characteristics showed no differences in age (AK mean 32.4±SD 5.3, P 32.0±5.7, p=0.314), body mass index (AK 29.5±5.8 kg/m^2, P 29.1±5.8 kg/m^2, p=0.328), week of gestation (AK 37.4±3 weeks, P 37.4±3 weeks, p=0.969), number of pregnancies (AK 2.2±1.2, P 2.3±1.3, p=0.090), number of deliveries (AK 0.9±1.0, P 1.0±1.1, p=0.057), comorbidities like pre-eclampsia (AK 8.4%, P 5.6%, p=0.107) or cardiovascular diseases (AK 4.3%, P 2.7%, p=0.192, see table 1). There was no significant difference in American Society of Anesthesiologists (ASA) classification between AK and P (p=0.950). Neonatal data elicited no difference in birth weight (AK 2951±787 g, P 2952±829 g, p=0.556), birth size (AK 49.6±4.7 cm, P 49.5±5.0 cm, p=0.621) and head circumference (AK 33.8±2.8 cm, P 33.8±2.9 cm, p=0.332, see table 1). Admission to PICU showed no differences (AK 20.5%, P 22.1%, p=0.560).

CS characteristics

Emergency cases were similar between the groups (AK 42.5%, P 37.9%, p=0.168), but significantly more procedures (p=0.016) were performed during on-call hours in AK group (34.3%) compared with P (26.7%). The time for induction of anaesthesia and time to delivery after SPA induction were similar (see table 2). There was no difference in blood loss (p=0.912), but less crystalloids (mean difference −247 mL, 95% CI

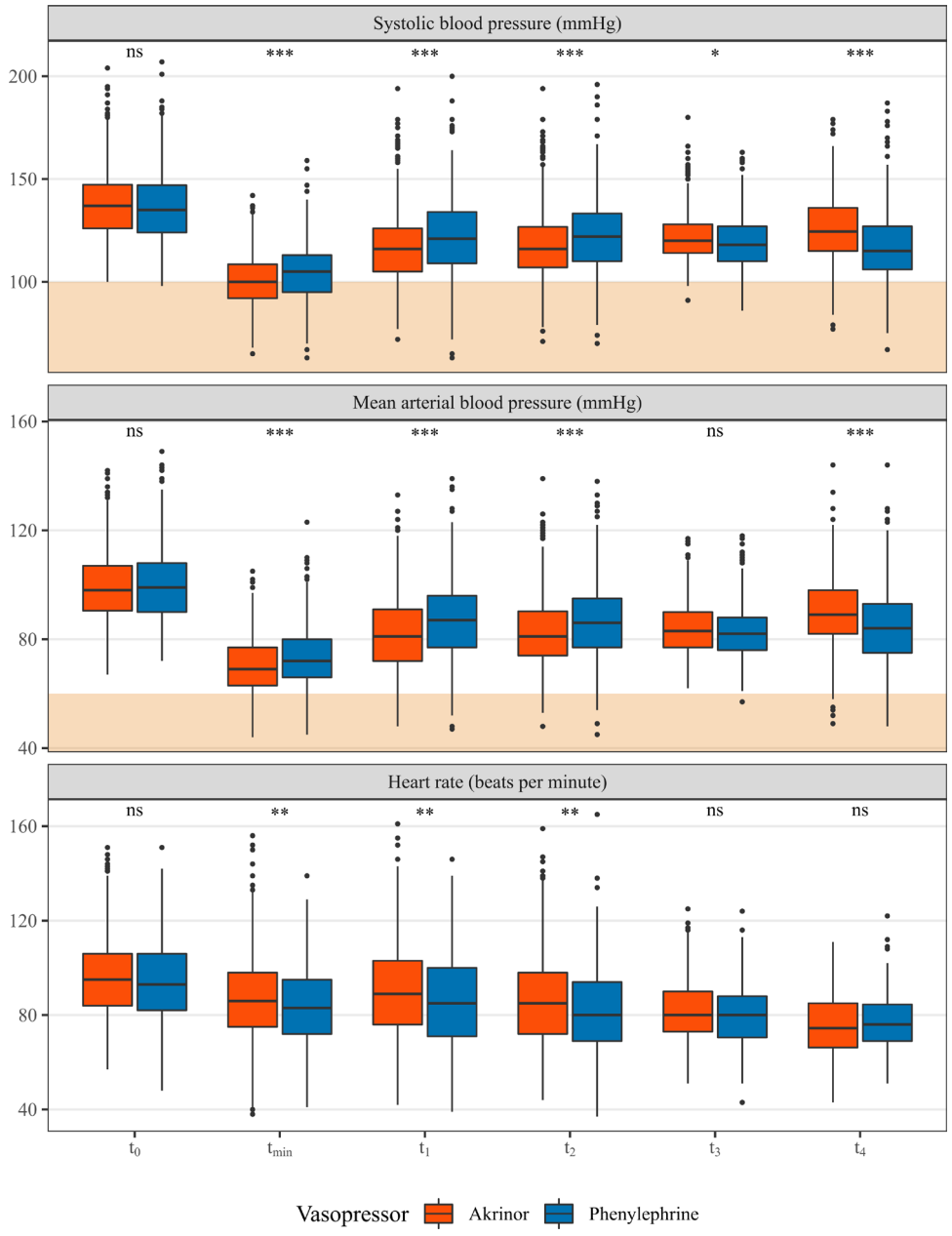

Figure 2 Maternal haemodynamics. Maternal systolic blood pressure (SBP), maternal mean arterial blood pressure and maternal heart rate shown in boxplots. Areas with SBP <100 mm Hg and mean arterial pressure (MAP) <60 mm Hg are highlighted in orange. t_0=first measurement in the OR; t_1=5 min after spinal anaesthesia induction; t_2=10 min after spinal anaesthesia (SPA) induction; t_3=last measurement in the OR; t_4=first measurement on the IMC; t_{min}=lowest SBP; box=IQR; horizontal line=median; whiskers=largest/smallest value no further than 1.5 × IQR, outliers plotted as separate data points. *P<0.05; **p<0.01; ***p<0.001. ns, not significant.

−362 to −133), but more colloids (mean difference 44 mL, 95% CI 26 to 63) were infused in AK (crystalloids 1952±791 mL/colloids 60±170 mL) compared with P (crystalloids 2199±887 mL/colloids 16±94 mL). Mean cumulative dose of AK was 5.6±3.8 mL (cafedrine hydrochloride 20 mg/mL and theodrenaline hydrochloride 1 mg/mL). In n=111 (25.2%), more than one vial was necessary. Cumulative AK dosage and minimal SBP t_{min} correlated significantly with r=−0.36 (95% CI −0.44 to −0.27) (p<0.001). Mean maximum infusion rate of P was 0.72±0.33 µg/kg/min. In n=199 (48.5%) cases, the maximum infusion rate was the default starting infusion rate with 0.5 µg/kg/min. In n=23 (5.6%) cases, the infusion rate was 1.5 µg/kg/min or greater. Maximum P dosage and minimal SBP t_{min} also correlated significantly with r=−0.42 (95% CI −0.50 to −0.34) (p<0.001). Rescue medication to stabilise BP or heart rate was 4.8 (95% CI 3.0 to 7.7) times more likely to be needed in P (21.8%) versus AK (4.5%). Antiemetic drugs were used in the same frequency in both cohorts (AK 18.2%, P 18.0%, p=0.933).

Table 3 Maternal systolic and mean arterial blood pressure

	Systolic blood pressure			Mean arterial blood pressure		
	Akrinor n=440	Phenylephrine n=412	P value	Akrinor n=440	Phenylephrine n=412	P value
t_0 (mm Hg)	137.7±17.2	136.6±17.7	0.268	99.2±13.3	99.6±13.9	0.695
t_1 (mm Hg)	117.0±19.4	121.8±19.9	<0.001	82.3±14.9	86.4±15.7	<0.001
0%–10% decline	159 (36.7)	209 (52.0)	<0.001	146 (33.9)	189 (47.0)	<0.001
10%–20% decline	133 (30.7)	115 (28.6)	0.505	121 (28.1)	103 (25.6)	0.425
20%–30% decline	84 (19.4)	45 (11.2)	0.001	89 (20.6)	63 (15.7)	0.063
<100 mm Hg	66 (15.1)	49 (12.0)	0.185			
<60 mm Hg				20 (4.6)	19 (4.6)	1.00
≥20% decline	145 (33.5)	79 (19.7)	<0.001	166 (38.5)	113 (28.1)	0.001
t_2 (mm Hg)	118.4±18.1	123.0±18.6	<0.001	83.1±13.7	86.9±14.9	<0.001
0%–10% decline	172 (39.6)	211 (52.8)	<0.001	143 (33.1)	172 (43.1)	0.003
10%–20% decline	144 (33.2)	112 (28.0)	0.105	131 (30.3)	125 (31.3)	0.754
20%–30% decline	76 (17.5)	53 (13.3)	0.089	100 (23.1)	65 (16.3)	0.013
<100 mm Hg	44 (10.0)	33 (8.1)	0.323			
<60 mm Hg				10 (2.3)	12 (2.9)	0.667
≥20% decline	119 (27.4)	77 (19.3)	0.005	162 (37.5)	103 (25.8)	<0.001
t_3 (mm Hg)	121.7±12.1	119.5±12.8	0.014	84.1±9.8	82.9±10.6	0.058
0%–10% decline	190 (43.7)	167 (41.4)	0.513	131 (30.2)	105 (26.1)	0.185
10%–20% decline	164 (37.7)	153 (38.0)	0.937	168 (38.7)	151 (37.5)	0.712
20%–30% decline	76 (17.5)	71 (17.6)	0.956	113 (26.0)	106 (26.3)	0.930
<100 mm Hg	6 (1.4)	18 (4.4)	0.008			
<60 mm Hg				0 (0)	1 (0.2)	0.484
≥20% decline	82 (18.9)	84 (20.8)	0.470	141 (32.5)	149 (37.0)	0.173
t_4 (mm Hg)	125.7±16.0	116.9±17.2	<0.001	89.8±13.1	84.4±13.3	<0.001
0%–10% decline	232 (53.3)	144 (35.7)	<0.001	217 (50.0)	138 (34.2)	<0.001
10%–20% decline	135 (31.0)	139 (34.5)	0.287	134 (30.9)	129 (32.0)	0.724
20%–30% decline	56 (12.9)	91 (22.6)	<0.001	61 (14.1)	88 (21.8)	0.003
<100 mm Hg	13 (3.0)	54 (13.1)	<0.001			
<60 mm Hg				5 (1.1)	10 (2.4)	0.195
≥20% decline	69 (15.9)	122 (30.3)	<0.001	85 (19.6)	139 (34.5)	<0.001
t_{min} (mm Hg)	100.6±13.1	105.0±14.5	<0.001	70.2±10.7	73.2±11.8	<0.001
0%–10% decline	25 (5.7)	44 (10.9)	0.007	28 (6.5)	31 (7.7)	0.489
10%–20% decline	101 (23.2)	140 (34.7)	<0.001	78 (18.0)	94 (23.3)	0.058
20%–30% decline	147 (33.8)	122 (30.3)	0.275	128 (29.6)	133 (33.0)	0.283
<100 mm Hg	205 (46.7)	133 (32.4)	<0.001			
<60 mm Hg				64 (14.6)	45 (10.9)	0.124
≥20% decline	312 (71.7)	222 (55.1)	<0.001	333 (76.9)	281 (69.7)	0.019

t_0=baseline, first measurement in the OR; t_1=5 min after spinal anaesthesia; t_2=10 min after SPA; t_3=last measurement in the OR; t_4=first measurement on the IMC; t_{min}=lowest SBP. Mean±SD, n (%), n=number of cases, p value test on difference between AK and P.

AK, Akrinor; IMC, Intermidate Care; P, phenylephrine; SBP, systolic blood pressure; SPA, spinal anaesthesia.

Maternal haemodynamics

Blood pressure

Maternal haemodynamics are summarised in figure 2 and for detailed numbers see table 3. Hypotension defined as ≥20% decrease in SBP occurred at t_{min} (point of time with lowest SBP) 1.3 (95% CI 1.2 to 1.4) times more often in AK (71.7%) than in P (55.1%), at t_1 (5 min after SPA induction) 1.7 (95% CI 1.3 to 2.2) times more often in AK (33.5%) than in P (19.7%) and at t_2 (10 min after SPA induction) 1.4 (95% CI 1.1 to 1.8) times more often with AK (27.4%) than with P (19.2%). If hypotension is defined as ≥ 20% decrease of MAP, it occurred 1.1 (95%

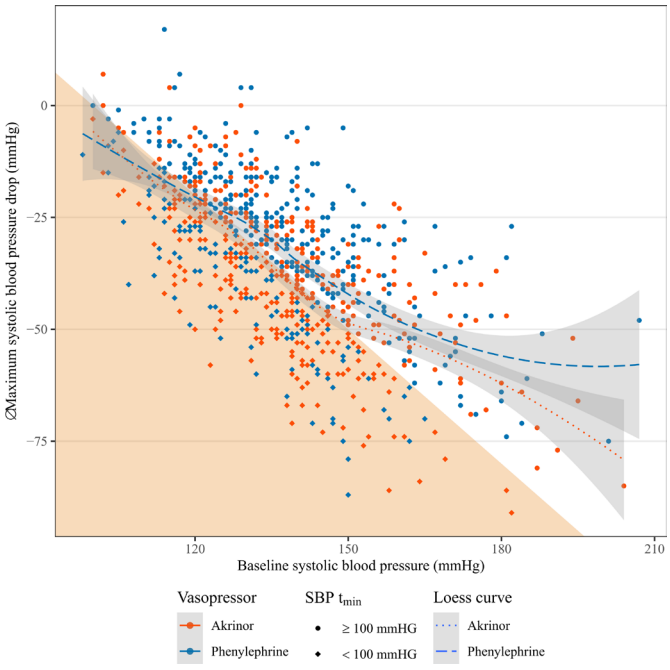

Figure 3 Maximal drop of systolic blood pressure (SBP) in dependence of baseline SBP. Function of maximum drop of SBP (SBP t_{min}–SBP t_0) against baseline SBP (SBP t_0) as a scatterplot. Overplotting may occur. Local regression curves (locally estimated scatterplot smoothing) for Akrinor (AK) and phenylephrine (P) are shown with 95% CI as grey areas. Area with SBP <100 mm Hg is marked in orange and data points with SBP <100 mm Hg are drawn in rhombus shape. There was a strong positive correlation between baseline SBP and maximum SBP drop (r=0.68, 95% CI 0.64 to 0.71). With baseline SBP values >120 mm Hg, P tends to have lower SBP drops than AK. With baseline SBP values <120 mm Hg the risk of SBP drops to values <100 mm Hg increases for both groups.

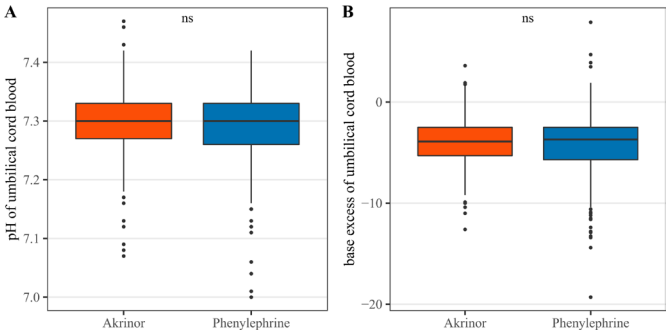

Figure 4 (A) Neonatal umbilical cord blood pH and (B) base excess values are drawn as boxplots. Box=IQR, horizontal line=median, whiskers=largest/smallest value no further than 1.5×IQR, outliers plotted as separate data points. ns, not significant.

CI 1.0 to 1.2) more often with AK (76.9 %) than with P (69.7 %) at tmin, 1.4 (1.1 to 1.7) times more often with AK (38.5 %) than with P (28.1 %) at t1 and 1.5 (1.2 to 1.8) times more often with AK (37.5 %) than with P (25.8 %) at t2. When hypotension is defined as SBP <100 mm Hg, at t_{min} it occurred more frequently in AK (46.7%) than in P (32.4%) (risk ratio 1.4, 95% CI 1.2 to 1.7) while there was no difference at t_1 (AK 15.1%, P 12.0%, risk ratio 1.3, 95% CI 0.9 to 1.8) and t_2 (AK 10.0%, P 8.1%, risk ratio 1.2, 95% CI 0.8 to 1.9). When hypotension is defined with MAP <60 mm Hg, there was no difference at t_{min} (AK 14.6%, P 10.9%, risk ratio 1.3, 95% CI 0.9 to 1.9), t_1 (AK 4.6%, P 4.6%, risk ratio 1.0, 95% CI 0.5 to 1.8) and t_2 (AK 2.3%, P 2.9%, risk ratio 0.8, 95% CI 0.3 to 1.8). As seen in figure 2, the mean difference of SBP between P and AK was t_{min} 4.4 mm Hg (95% CI 2.6 to 6.3), t_1 4.7 mm Hg (95% CI 2.1 to 7.4), t_2 4.6 mm Hg (95% CI 2.1 to 7.1), and for MAP t_{min} 3.0 mm Hg (95% CI 1.5 to 4.5), t_1 4.1 mm Hg (95% CI 2.1 to 6.2), t_2 3.8 mm Hg (95% CI 1.9 to 5.7). Interestingly, the risk for low SBP <100 mm Hg at t_4 (first measurement on IMC) was 4.4 (95% CI 2.5 to 8.0) times higher in P group (13.1%) compared with AK (3.0%). Figure 3 shows the maximum SBP drop in function of baseline (t_0) SBP level. There was a positive correlation between baseline SBP and drop of SBP (r=0.68, 95% CI 0.64 to 0.71, p<0.001). With baseline SBP over 120 mm Hg, the prophylactic application of P led to slightly lower SBP drops. When baseline SBP was <120 mm Hg the risk of SBP drop below 100 mm Hg increased when using P (from 27.8% to 54.4%, risk ratio 2.0, 95% CI 1.5 to 2.6) as well as when using AK (from 43.0% to 70.7%, risk ratio 1.5, 95% CI 1.2 to 1.9).

Heart rate

Baseline values were similar between groups (AK 96.2±17.6 min^{-1}, P 94.8±17.7 min^{-1}, p=0.297). Heart rate was slightly higher with AK at t_{min} (mean difference 3.5 min^{-1}, 95% CI 1.1 to 6.0), t_1 (mean difference 4.7 min^{-1}, 95% CI 1.9 to 7.4) and t_2 (mean difference 4.0 min^{-1}, 95% CI 1.4 to 6.5) (see also figure 2). Anticholinergic drugs were given 3.0 (95% CI 1.8 to 5.0) times more often in P (12.1%) than in AK (4.1%) (table 2).

Newborn values

There was no difference in umbilical arterial cord pH (AK 7.30±0.05, P 7.29±0.06, p=0.150) and base deficit (base excess) levels (AK −4.0±2.3, P −4.2±3.1, p=0.936) (figure 4). Fetal acidosis (pH <7.2) was 2.8 (95% CI 1.4 to 5.6) times more likely to occur with P (6.5%) than with AK (2.3%). Apgar scores showed significant differences in minute 1 (AK 8.3±1.6, P 8.0±1.8, p=0.017) and minute 5 (AK 9.3±1.3, P 9.2±1.3, p=0.023) and no difference in minute 10 (AK 9.6±1.0, P 9.6±0.9, p=0.381) (table 4).

DISCUSSION

The aim of this study was to compare the internationally established standard P with the most widely used vasopressor in Germany, the mixture of cafedrine and theodrenaline (AK), to treat SMH for elective or emergency CS.[9] Currently, P serves as the first-line choice to treat SMH internationally.[7] AK is used up to 86% to treat SMH, and P is not regularly available in Germany.[9] The explanation for this is a currently restricted approval

Table 4 Apgar values

	n=852	Akrinor (AK) n=440	Phenylephrine (P) n=412	P value
Apgar minute 1	848	8.3±1.6	8.0±1.8	*
Reassuring (7–10)		383 (87.4)	343 (83.7)	ns
Moderately abnormal (4–6)		42 (9.6)	50 (12.2)	ns
Concerning (0–3)		13 (3.0)	17 (4.1)	ns
Apgar minute 5	848	9.3±1.3	9.2±1.3	*
Reassuring (7–10)		416 (95.0)	385 (93.9)	*
Moderately abnormal (4–6)		19 (4.3)	22 (5.4)	ns
Concerning (0–3)		3 (0.7)	3 (0.7)	ns
Apgar minute 10	848	9.6±1.0	9.6±0.9	ns
Reassuring (7–10)		428 (97.7)	404 (98.5)	ns
Moderately abnormal (4–6)		9 (2.1)	5 (1.2)	ns
Concerning (0–3)		1 (0.2)	1 (0.2)	ns

Mean±SD, n (%), n=number of cases, p value difference between AK and P.
*P<0.05.
ns, not significant.

for AK only in Germany, Austria and Switzerland. For a detailed pharmacological description of AK, see review.[10]

The key findings are: (1) reactive AK bolus therapy had lower BP levels with questionable clinical relevance; (2) prophylactic P infusion was correlated with higher usage of rescue medication; (3) neonatal outcomes were comparable in both groups, but P possibly could lead more often to pH levels <7.2; (4) the first BP measurements on IMC were significantly higher in the AK group; and (5) women with baseline SBP <120 mm Hg may have a high risk to drop below 100 mm Hg during CS.

One major problem is the heterogeneous definition of SMH.[13] SBP <100 mm Hg or a decrease of 20% in baseline SBP is commonly used to define SMH. We chose the first measurement in the OR as baseline BP t_0. Stress and anxiety may explain the high levels of BP t_0 (137 mm Hg SBP or 99 mm Hg MAP). Therefore, a 20% drop may still allow normal placental perfusion and generate sufficient (or even normal) maternal and fetal organ perfusion (20% reduction is 110 mm Hg SBP and 79 mm Hg MAP). Luther *et al* could show a significant increase in SBP in the OR compared with measurements on the morning before CS.[14] We judge the statistically significant differences of SBP levels in our trial (maximum mean difference was at t_1 4.7 mm Hg) between the groups in the OR as mostly clinically irrelevant. Recent data showed that <120 mm Hg baseline SBP was associated with an increased risk for hypotension.[15] This is in line with our data, which also demonstrate an increase in risk to drop below 100 mm Hg SBP when baseline SBP is <120 mm Hg. However, SBP poorly correlates with organ perfusion in comparison to MAP, and MAP <60 mm Hg did not differ between groups. Over both groups, incidence of MAP <60 mm Hg was 12.8% compared with 39.8% SBP <100 mm Hg at t_{min}. Since intraoperative vital parameters were extracted from handwritten anaesthesia records and often were only recorded in 5 min intervals, there may be a bias limiting the power of this analysis. Although the moment of lowest SBP (t_{min}) occurred most often right after anaesthesia induction, it was not restricted to the period until delivery (eg, haemorrhage). Also, the recorded medication was not restricted to the period until delivery. Because of this, maternal haemodynamics at t_{min} and the overall applied medication may not be able to have any effect on the fetus in some cases. A major problem is the lack of animal models. In our opinion, only primates can serve as an adequate animal model to investigate SMH. In comparison to a human placenta, the placental anatomy of sheep, dogs, swine, rats, etc is different. Ephedrine showed superior results in sheep, but revealed more umbilical arterial acidosis in humans compared with P.[16] Therefore, translation of animal trials to human care is really difficult or virtually impossible. Thus, the impact of maternal hypotension on human fetal physiology during CS is poorly characterised so far. Duration of SMH may be more important than severity. Hypotension for less than 2 min may not affect neonatal neurobehavioural outcome.[17] Data showed that a transient reduction of BP (drop of 30 or below 100 mm Hg SBP) did not affect neonatal Apgar scores, the need of oxygen supply or incidence of meconium-stained amniotic fluid.[18] Duration of more than 2 min of SMH, however, has led to increased umbilical venous oxypurines and lipid peroxidase, which can be interpreted as an ischaemia/reperfusion injury. More than 4 min of SMH was associated with neurobehavioural changes. Our data unfortunately do not lead to a reliable statement concerning differences in the duration of SMH.

In regard to the fetal primary outcome in our trial, there were no differences in arterial umbilical cord pH and base deficit overall. P is more often recommended than ephedrine, because P showed less severe umbilical

cord acidosis. Interestingly, in our trial, pH <7.2 was significantly more often detected in P (n=26 (6.5%)) compared with AK (n=10 (2.3%)). APGAR scores showed significant improvement in AK but again with doubtable clinical relevance.

There is evidence to suggest that a decrease in maternal heart rate correlates with a reduction of CO.[19 20] CO in turn better correlates with uteroplacental blood flow and furthermore with fetal acidosis than SBP.[21] Therefore, one could conclude that the use of P correlated with a higher rate of fetal acidosis following significantly more episodes of bradycardia. Interestingly, there was no correlation between dosage of P and fetal acidosis in our study. In addition to CO, BP depends on blood volume and vascular resistance. Hypovolaemia (relative) is one possible explanation for SMH. A significant difference in volume status between the groups can be excluded, because the blood loss was equal in both groups overall and our data showed only a small difference in volume substitution most likely due to the retrospective character and the stop of routine use of colloids. However, one limitation of the study is the lack of data on how preloading or coloading was performed, and therefore we interpreted the 60 mL colloid difference neither as coload nor clinically relevant dosage. Another limitation is the different way of application of P and AK. P was prophylactically started with a syringe pump after induction of SPA whereas the application of AK was reactively as decided by the treating physician. AK is easily given as bolus and may reduce medication errors mainly in an emergency situation. This may explain higher physician satisfaction when AK was used for CS in another trial.[22] P was exclusively used in the obstetric OR for CS in our hospital. Therefore, the physicians reduced experience with P compared with the more routine usage of AK and norepinephrine may be a bias in this investigation. There does not exist any data for equivalent dosage of P compared with AK. Thus, an underdosage of P cannot be excluded in comparison to AK and therefore an increase in the usage of rescue medication in the P group. 7.8% of the women did not receive any vasopressors and there was a reduction over the years because P was established as standard operating procedure (2014: 6% to 2016: 1.3%) (mainly P used). This may explain the reduction of the no use of vasopressors in 2016, but raises the question of an estimated 4.7% overtreatment in the P group.

Postoperative hypotension can also induce major complication like AKI or increase 30-day mortality.[23] The AK group demonstrated less often hypotension <100 mm Hg SBP when arriving at the IMC and may have advantages for postoperative care due to longer lasting effects. These data bring up another focus of hypotension therapy for CS and may reduce major complication postoperative, especially for women with a higher ASA classification.

CONCLUSION

Because prophylactic P infusion was not superior to AK bolus therapy in our clinical set-up, showed more often severe umbilical arterial pH levels, increased usage of additional medication (vasopressor and/or parasympatholytics) and is more expensive, we stopped using P for the treatment of spinal-induced maternal hypotension in our hospital. Irrespective of the mode of vasopressor, if baseline SBP is 120 mm Hg or below, patients are at high risk to develop hypotension below 100 mm Hg systolic after SPA.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Ethical Committee of the Albert Ludwig University (ethical committee number: 20-1327) of Freiburg, Germany (Chairperson Professor Dr R Korinthenberg) on 26 January 2021. All data sets were anonymised before statistical evaluation. The study complied with the latest version of the Declaration of Helsinki (German Clinical Trials Register: DRKS00025795).

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