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Evidence That Intravenous Vasopressors Can Affect Rostral Spread of Spinal Anesthesia in Pregnancy

David W. Cooper, F.R.C.A., Leo Jeyaraj, F.R.C.A.,† Ryan Hynd, M.B. B.Ch.,† Rebekah Thompson, F.R.C.A.,† Tim Meek, F.R.C.A.,* David M. Ryall, F.R.C.A.,* Manmohan S. Kokri, F.R.C.S., F.R.C.A.**

Background: **The authors have previously observed an apparent association between rostral spread of spinal anesthesia and choice of intravenous vasopressor given to maintain maternal systolic arterial pressure during cesarean delivery. This study tested the hypothesis that an intravenous infusion of phenylephrine can reduce rostral spread of spinal anesthesia in pregnancy, compared with ephedrine.**

Methods: **The study was randomized and double blind. It compared phenylephrine 100 μg/ml (phenylephrine group, n = 30), and ephedrine 3 mg/ml (ephedrine group, n = 30), given by infusion, to prevent maternal hypotension during combined spinal–epidural anesthesia for cesarean delivery. Two ml intrathecal plain levobupivacaine, 0.5%, combined with 0.4 ml intrathecal fentanyl, 50 μg/ml, and 10 ml epidural saline was given with the patient in the sitting position. The upper level of neural blockade to cold and light touch sensation was recorded at 10 and 20 min postspinal. Epidural space pressure was recorded at 5, 10, 15, and 20 min.**

Results: **At 20 min, the upper dermatome blocked to cold sensation was median T3 (interquartile range, T2–T4) for the phenylephrine group, compared with T1 (T1–T2) for the ephedrine group ($P = 0.001$). At 20 min, the upper dermatome blocked to light touch sensation was median T5 (T4–T8) for the phenylephrine group, compared with T3 (T2–T6) for the ephedrine group ($P = 0.009$). The mean epidural space pressure in the phenylephrine group was 16 (13–19) mmHg, compared with 16 (13–18) mmHg in the ephedrine group ($P = 0.63$).**

Conclusions: **This study provides evidence that intravenous phenylephrine can decrease rostral spread of spinal anesthesia in pregnancy, compared with intravenous ephedrine. Further work is required to investigate possible mechanisms and to assess its clinical significance.**

WE have previously observed an apparent association between rostral spread of spinal anesthesia and choice of intravenous vasopressor given to maintain maternal systolic arterial pressure during cesarean delivery.[1] This study tested the hypothesis that an intravenous infusion of phenylephrine can reduce rostral spread of spinal anesthesia in pregnancy, compared with ephedrine. During the first 20 min of a combined spinal–epidural anesthetic for elective cesarean delivery, rostral spread of neural blockade to cold and light touch sensation was assessed when either phenylephrine or ephedrine was used as the first-line vasopressor.

If phenylephrine can reduce rostral spread of spinal anesthesia in pregnancy, a possible mechanism could be greater epidural vein constriction with phenylephrine than with ephedrine, thereby reducing epidural vein engorgement. If so, phenylephrine may be associated with a decrease in epidural space pressure, compared with ephedrine. Lumbar epidural space pressure was therefore measured during the study.

Materials and Methods

The local hospital ethics committee approved this randomized, double-blind study. After obtaining written informed consent, we studied patients with American Society of Anesthesiologists physical status I and II who were scheduled to undergo elective cesarean delivery during spinal anesthesia. Women with a singleton pregnancy, no known fetal abnormality, and no history of preeclampsia or diabetes mellitus were included.

Before coming to the anesthetic room, patients had three arterial pressure and heart rate readings recorded with an automated oscillometer, at 3-min intervals, while sitting in bed. The lowest of the three readings was recorded as the baseline value for the maternal systolic arterial pressure and heart rate.

Patients were randomly allocated by envelope selection to one of two vasopressor solutions to maintain maternal systolic arterial pressure during spinal anesthesia. The patients, anesthetists, and nurses involved with patient care were blinded to the patient grouping. The phenylephrine group received 100 μg/ml phenylephrine, and the ephedrine group received 3 mg/ml ephedrine. The concentrations were the same as those used in a previous study at this hospital.[2] A syringe of rescue vasopressor solution containing 10 ml phenylephrine, 100 μg/ml, combined with 3 mg/ml ephedrine, was also prepared.

Immediately before spinal anesthesia, 10 mg intravenous metoclopramide, 0.2 mg glycopyrrolate, and 10 ml/kg Hartmann's solution were given. A combined spinal epidural anesthetic was performed at L3–L4, with the patient in the sitting position, using a pencil point spinal needle passed through a 16-gauge epidural Tuohy needle. The epidural space was detected by using loss of resistance to air or saline, according to the anesthetist's preference, with less than 2 ml being injected into the epidural space. Two ml intrathecal plain levobupivacaine, 0.5%, combined with 0.4 ml fentanyl, 50 μg/ml, was injected over 10–15 s, with the bevel rostral. Ten

* Consultant Anaesthetist, † Specialist Registrar Anaesthetist.

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Address correspondence to Dr. Cooper: Department of Anaesthesia, James Cook University Hospital, Middlesbrough, Cleveland TS4 3BW, United Kingdom. Address electronic mail to: david.cooper@stees.nhs.uk. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

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milliliters epidural saline was then given *via* the Tuohy needle over 10–15 s to enhance spread of the spinal solution[3–5] and to reduce the risk of the epidural catheter entering an epidural vein.[6] A 16-gauge epidural catheter (Sims Portex Limited, Hythe, Kent, United Kingdom) was then passed, leaving 5 cm in the epidural space. After an aspiration test, the epidural catheter was attached to a bacterial filter (Sims Portex Limited), which had been flushed with saline. As soon as a sterile dressing had been placed over the skin puncture site, the patient was placed in the left lateral position, and further tape was applied to secure the epidural catheter. The patient was then placed in the supine position, with standard left lateral tilt, and 1 ml saline was injected through the catheter to check patency.

Immediately after the spinal injection, an infusion of intravenous vasopressor trial solution was started, using an IVAC P2000 infusion pump (Alaris Medical Systems, Basingstoke, Hants, United Kingdom), and adjusted according to a standard protocol. Systolic arterial pressure and heart rate were measured every minute after spinal anesthesia, using the same automated oscillometer that was used for the baseline arterial pressure. The trial solution was started at 40 ml/h (equating to 67 μg/min phenylephrine for the phenylephrine group and 2 mg/min ephedrine for the ephedrine group). The rate was changed by factors of two, as necessary, to maintain systolic arterial pressure at baseline. The maximum infusion rate in the protocol was 40 ml/h, and the minimum rate was 2.5 ml/h (if less was required, the infusion was discontinued and recommenced as necessary). If the systolic arterial pressure increased above 1.20 times baseline, the infusion was stopped and recommenced at half the rate, when the systolic arterial pressure had decreased below 1.20 times baseline. If the systolic arterial pressure decreased below 0.80 times baseline, 1-ml boluses of the rescue vasopressor solution (100 μg phenylephrine, 3 mg ephedrine) were given as required to increase the pressure above 0.80 times baseline.

Maternal heart rate was continuously measured with a pulse oximeter and an electrocardiograph. Further intravenous glycopyrrolate, 0.2 mg, was given for inappropriate or severe bradycardia according to a protocol that included systolic arterial pressure. It was given if maternal heart rate was less than 60 beats/min and systolic arterial pressure was less than 0.80 times baseline; if heart rate was less than 50 beats/min and systolic arterial pressure was less than 1.00 times baseline; or if heart rate was less than 45 beats/min, whatever the systolic arterial pressure.

The study continued for 20 min after spinal anesthesia. Epidural space pressure was recorded at 5, 10, 15, and 20 min after spinal anesthesia. An Eschmann J3 operating table (Eschmann Equipment, Lancing, West Sussex, United Kingdom) was used for all patients. Before the patient was positioned on the operating table, a spirit level was used to level it in the longitudinal and transverse planes. A PX-260 pressure transducer (Edwards Lifesciences, LLC, Irvine, CA), which was flushed with normal saline and zeroed to atmospheric pressure, was attached to the same point on the operating table for each patient. Standard left lateral tilt was achieved by turning the lateral tilt handle exactly five full turns. The vertical height from the midpoint of the top of the operating table to the pressure transducer, plus the depth of the epidural space for each patient, was used to correct the pressure measured to that at the level of the epidural space. The initial pressure reading was not recorded for at least 1 min after the epidural catheter was flushed and connected to the transducer, to allow the pressure to equilibrate. Pressure was measured through a static column of saline (*i.e.*, no constant flush was used) to avoid a pressure gradient developing across the resistance to flow in the epidural catheter and filter.

Block height was measured at 10 and 20 min after spinal anesthesia. Ethyl chloride spray was used to assess cold sensation (awareness of the spray being cold) and light touch sensation (awareness of the spray). At 20 min, the volume of vasopressor given by infusion and the volume of vasopressor given from the rescue syringe were recorded. The study stopped at 20 min after spinal anesthesia.

Statistical Analysis

We have previously observed an incidence of cervical-level neural blockade to cold sensation of none of 13 patients when phenylephrine was given to maintain maternal systolic arterial pressure, compared with 7 of 14 (incidence, 50% [95% confidence interval, 24–76%]) when ephedrine was given,[1] using the combined spinal–epidural anesthetic technique described in this study. None of an additional 17 patients given phenylephrine, who had the same anesthetic technique, had cervical-level blockade (unpublished data from routine practice).

The study was designed to have an 80% chance of detecting a 24% incidence of cervical-level neural blockade to cold sensation in the ephedrine group, compared with 0% in the phenylephrine group, at $P = 0.05$ (two sided). The Mann–Whitney U test and regression analysis were used to compare data. $P < 0.05$ was considered significant.

Results

Thirty patients were studied in the phenylephrine group, and 30 were studied in the ephedrine group. The groups were well matched for age, height, weight, gestation, breech presentation, previous cesarean delivery, and fetal weight (table 1). They were also well matched for baseline systolic arterial pressure and heart rate (table 1). The doses of vasopressor used in each group are

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Table 1. Maternal and Fetal Demographic Data, and Baseline Hemodynamic and Nausea Data

	Phenylephrine Group (n = 30)	Ephedrine Group (n = 30)
Age, yr	29 (24–34)	28 (22–31)
Height, cm	163 (157–169)	162 (160–165)
Weight, kg	75 (66–83)	80 (71–86)
Body mass index, kg/m^2	29 (25–32)	31 (28–35)
Previous cesarean delivery	69%	55%
Gestation, weeks	39 (39–39)	39 (38–39)
Breech presentation	34%	38%
Fetal weight, kg	3.39 (3.11–3.76)	3.24 (3.02–3.89)
Systolic arterial pressure, mmHg	114 (107–123)	112 (103–121)
Heart rate, beats/min	87 (78–93)	85 (81–92)

Data are expressed as proportion or median (interquartile range).

shown in table 2. Results are expressed as median (interquartile range). Loss of resistance to air was used for seven patients in each group.

The mean systolic arterial pressure was similar for both the phenylephrine and ephedrine groups, but the lowest systolic arterial pressure recorded was higher in the phenylephrine group than in the ephedrine group (table 2). The mean maternal heart rate and the incidence, severity, and duration of tachycardia was lower in the phenylephrine group than in the ephedrine group (table 2).

At 10 and 20 min postspinal, the level of neural blockade to cold and to light touch sensation was lower in the phenylephrine group than in the ephedrine group (figs. 1 and 2). Only 20% of patients in the phenylephrine group had neural blockade to cold sensation above T2, compared with 53% in the ephedrine group ($P = 0.008$). However, there was no significant difference in the incidence of cervical-level neural blockade between the groups. Two phenylephrine group patients had a cervical level of neural blockade to cold sensation (at C8), compared with six of the ephedrine group (three at C8 and three at C6) ($P = 0.13$).

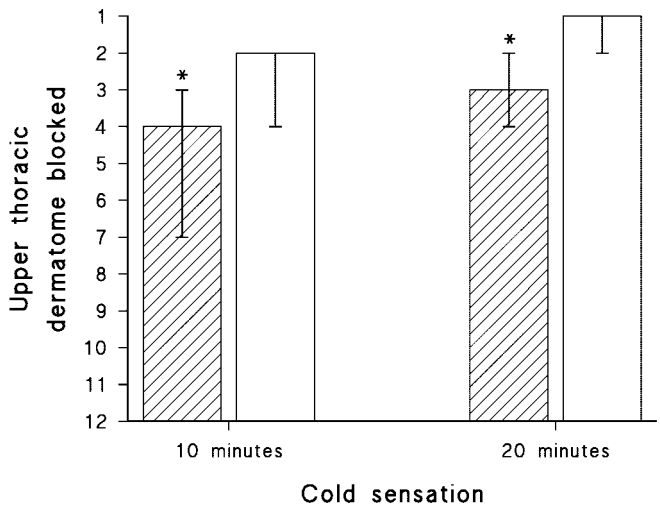

Fig. 1. Upper dermatome blocked to cold sensation at 10 and 20 min postspinal for the phenylephrine group (*cross-hatched bars*) and the ephedrine group (*open bars*). Data are expressed as median (interquartile range). There was a difference between the groups at 10 min ($P = 0.01$) and at 20 min postspinal ($P = 0.001$) (Mann–Whitney U test).

The epidural space pressure was similar for both groups. The mean epidural space pressure in the phenylephrine group was 16 (13–19) mmHg, compared with 16 (13–18) in the ephedrine group ($P = 0.63$). There was no correlation between epidural space pressure and body mass index ($r^2 = 0.00$, $P = 0.87$) or fetal weight

Table 2. Vasopressor and Hemodynamic Data from Spinal Anesthesia—20 Minutes

	Phenylephrine Group (n = 30)	Ephedrine Group (n = 30)	*P* Value
Vasopressor volume and dose			
Infusion volume, ml	9.2 (6.8–12.7)	12.9 (8.5–13.9)	0.020
Phenylephrine with ephedrine rescue solution volume, ml	0 (0–1)	1 (0–2)	0.023
Total phenylephrine dose, mg	0.97 (0.68–1.28)	0.10 (0.00–0.20)	<0.0001
Total ephedrine dose, mg	0.0 (0.0–3.0)	39.2 (29.5–43.9)	<0.0001
SAP			
Mean SAP as proportion of baseline	103% (99–108)	102% (94–105)	0.36
Highest SAP as proportion of baseline	122% (109–136)	120% (111–131)	0.40
Hypertension (SAP > 1.20 times baseline)	60%	47%	0.30
Proportion of readings > 1.20 times baseline	5% (0–17)	0% (0–15)	0.36
Lowest SAP as proportion of baseline	87% (76–93)	75% (71–87)	0.026
Hypotension	40%	63%	0.073
Proportion of readings < 0.80 times baseline	0% (0–10)	6% (0–11)	0.11
Heart rate			
Mean heart rate as proportion of baseline	86% (81–95)	110% (96–122)	< 0.0001
Highest heart rate as proportion of baseline	97% (88–109)	113% (101–128)	0.001
Tachycardia (heart rate > 100 beats/min)	43%	80%	0.004
Proportion of readings > 100 beats/min	0% (0–11)	30% (5–51)	0.0002
Bradycardia	0%	0%	1.0

Data are expressed as proportion or median (interquartile range).

SAP = systolic arterial pressure.

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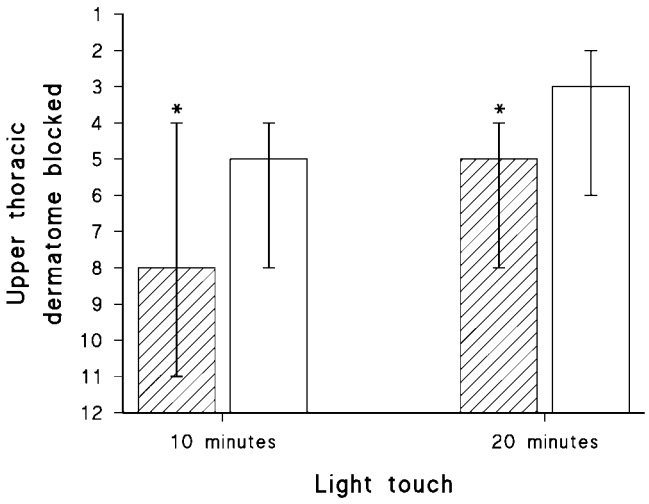

Fig. 2. Upper dermatome blocked to light touch sensation at 10 and 20 min postspinal for the phenylephrine group (*cross-hatched bars*) and the ephedrine group (*open bars*). Data are expressed as median (interquartile range). There was a difference between the groups at 10 min ($P = 0.026$) and at 20 min postspinal ($P = 0.009$) (Mann–Whitney U test).

($r^2 = 0.01$, $P = 0.58$). There was no correlation between epidural space pressure and the upper dermatome blocked to cold at 20 min ($r^2 = 0.02$, $P = 0.29$) or the upper dermatome blocked to light touch at 20 min ($r^2 = 0.00$, $P = 0.66$).

Discussion

This study found evidence that when intravenous phenylephrine was used to maintain systolic arterial pressure, it decreased rostral spread of neural blockade to cold and light touch sensation at 10 and 20 min postspinal, compared with ephedrine. This supports the hypothesis that an intravenous infusion of phenylephrine can reduce rostral spread of spinal anesthesia in pregnancy, compared with ephedrine.

We performed the study because a review of data from a previous study at our hospital found the incidence of cervical-level neural blockade to cold sensation to be lower with phenylephrine than with ephedrine.[1,2] In the previous study, none of 48 patients given a prophylactic phenylephrine infusion during spinal anesthesia for cesarean delivery had a cervical level of neural blockade to cold sensation, compared with 14 of 50 given ephedrine. Of the 14 patients with cervical-level blockade to cold sensation, it was above C4 for 6 of them. Cervical blockade was not associated with respiratory difficulty, but unpublished data from that study suggests that it may have been clinically significant. Within the ephedrine group, patients with cervical blockade had a greater incidence of hypotension (93% compared with 58%; $P = 0.02$), a 64% increase in ephedrine requirements ($P = 0.02$), and a greater incidence of fetal acidosis (46% compared with 11%; $P = 0.009$), despite similar maternal and fetal demographic data and uterine incision-delivery intervals.

In this follow-up study, the incidence of blockade to cold sensation above T2 was lower in the phenylephrine group than the ephedrine group, but there was only a trend toward a difference in the incidence of cervical blockade. We may not have found a difference in cervical blockade between the groups because of differences in the protocol for the administration of vasopressor solution between the two studies. To minimize the risk of severe hypotension (systolic arterial pressure less than 0.60 times baseline) in this study, which we had encountered in our previous study, changes were made to the protocol. The initial dose rate of vasopressor infusion was doubled, and because phenylephrine and ephedrine are additive,[2] a combination of both was given as a rescue solution. These protocol changes resulted in 18 of 30 ephedrine group patients (60%) also receiving phenylephrine, compared with only 2 of 50 (4%) in our previous study. The increased use of phenylephrine in the ephedrine group in this follow-up study may explain why the incidence and height of cervical-level neural blockade to cold sensation was not as great as we had expected.

How could intravenous vasopressor affect the spread of spinal anesthesia in pregnancy? We suggest that a possible mechanism could be that when phenylephrine and ephedrine are given in equally effective doses, venous tone is greater with phenylephrine. Phenylephrine is a directly acting α-adrenergic agonist, whereas ephedrine is an indirectly acting α- and β-adrenergic agonist. Spinal anesthesia decreases right atrial pressure because of vasodilatation secondary to sympathetic blockade.[7–11] Alpha agonists, such as phenylephrine, are more effective than ephedrine at increasing right atrial pressure during spinal anesthesia.[9–11] Further evidence that venous tone is greater with phenylephrine than with ephedrine comes from a study that examined the hemodynamic effects of phenylephrine and ephedrine given during spinal anesthesia for cesarean delivery.[12] It showed that for a similar systolic arterial pressure and cardiac output, heart rate was lower with phenylephrine than with ephedrine. This implies that for a similar systolic arterial pressure, stroke volume was greater with phenylephrine than with ephedrine, secondary to a greater right atrial pressure.

In nonpregnant patients, smaller volumes of lumbosacral cerebrospinal fluid (CSF) are associated with greater spread of spinal anesthetic.[13,14] Pregnancy increases the volume of epidural veins,[15] and caval compression causes further epidural vein engorgement.[16] A probable mechanism by which rostral spread of spinal anesthetic is increased in pregnancy is a reduction in lumbosacral CSF volume, secondary to compression of the dura by distended epidural veins. There is evidence that a rela-

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tively small increase in the volume of the epidural space (*e.g.*, injection of 10 ml epidural saline) can increase spread of spinal anesthesia in pregnant and nonpregnant patients.[3–5] Phenylephrine may reduce the enhanced spread of spinal anesthesia by constricting epidural veins to a greater degree than ephedrine, thereby reducing epidural vein engorgement.

We suggest another possible mechanism by which increased venous tone with phenylephrine may affect spread of spinal anesthesia. Changes in intracranial pressure cause compensatory shifts of CSF between the rigid cranial cavity and the more compliant vertebral canal. It is therefore possible that changes in right atrial pressure caused by caval compression, spinal anesthesia, or phenylephrine can influence the distribution of CSF between the cranial cavity and the vertebral canal. Caval compression increases pressure in the distal inferior vena cava, but it decreases right atrial pressure.[17] This (in conjunction with spinal anesthesia) would be expected to decrease internal jugular vein and therefore intracranial pressure, causing an intracranial shift of CSF. Conversely, a significant increase in right atrial pressure, caused by phenylephrine-induced venoconstriction, would increase intracranial pressure, possibly causing a significant shift of CSF from the cranial cavity to the vertebral canal. This may be a mechanism by which phenylephrine can reduce rostral spread of spinal anesthesia. Further studies are required to investigate the hypothesis that changes in right atrial pressure caused by caval compression, spinal anesthesia, or vasopressors can influence spread of spinal anesthesia.

A secondary hypothesis was that if phenylephrine constricted epidural veins to a greater degree than ephedrine, the epidural space pressure would be lower with phenylephrine than with ephedrine. Epidural space pressure is an indirect measure of subarachnoid and intracranial pressure because pressure equalizes across the moveable dura.[18–20] However, epidural space pressure was similar in both groups. This may be because the subarachnoid space is relatively compliant. Phenylephrine-induced changes in the distribution of CSF, which were large enough to affect spread of spinal anesthesia, may have been associated with changes in epidural space pressure that were too small to detect. There is evidence that the subarachnoid space is very compliant in pregnancy. Caval compression, which increases the volume of epidural veins, does not seem to be associated with an increase in epidural space pressure. Epidural space pressure does increase on moving from the lateral to the supine position, but the change is similar in pregnant and nonpregnant patients.[21] Another study found that the injection of 15 ml bupivacaine into the epidural space produces a greater increase in epidural space pressure than 10 ml, but the effect is short lived.[22] Furthermore, we did not observe an association between variables that may be associated with increased caval compression (maternal body mass index and fetal weight) and epidural space pressure.

To increase the chance of finding a difference in rostral spread of spinal anesthesia between the two groups, we chose the anesthetic technique from our previous study that was associated with the greatest difference in the incidence of cervical blockade. As part of the technique, 10 ml saline was injected through the Tuohy needle. The purpose of this was to enhance spread of spinal anesthetic[3–5] and to reduce the chance of the epidural catheter entering an epidural vein.[6] This may have altered epidural space pressure/compliance or altered the vasoreactivity of the epidural vessels. Therefore, our results cannot be extrapolated to other more commonly used techniques that do not involve epidural volume enhancement. However, review of our previous data does suggest that phenylephrine reduces cervical spread of 0.5% spinal hyperbaric bupivacaine given without epidural volume enhancement in the sitting position, compared with ephedrine.[1]

In conclusion, this study provides evidence that intravenous phenylephrine can decrease rostral spread of spinal anesthesia in pregnancy, compared with intravenous ephedrine. Further work is required to investigate possible mechanisms and to assess its clinical significance.

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