

**Maternal cardiac output response to vasopressor during
spinal anaesthesia for caesarean section in patients with
severe preeclampsia**

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List of abbreviations

BP	Blood pressure
SB	Systolic blood pressure
DBP	Diastolic blood pressure
MAP	Mean arterial blood pressure
SVR	Systemic vascular resistance
SVRI	Systemic vascular resistance index
SV	Stroke volume
HR	Heart Rate
CO	Cardiac output
CI	Cardiac Index
CS	Caesarean section
SA	Spinal Anaesthesia
SD	Standard deviation
E	Ephedrine
P	Phenylephrine
HELLP	Haemolysis, elevated liver enzymes, low platelets

Part A: Study protocol

Maternal cardiac output response to vasopressor during spinal anaesthesia for caesarean section in patients with severe preeclampsia

Introduction

Preeclampsia is a complex multisystem disorder of a poorly understood etiology, which complicates 8-12 % of pregnancies.^{1,2,3} A recent Lancet review, May 2014, has shown that hypertensive disorders in pregnancy is the second most common cause of maternal death, leading cause being haemorrhage.¹ Many preeclamptic patients require caesarean section for delivery of the infant. In the absence of contraindications, neuraxial anaesthesia is preferred for caesarean delivery; due to problems related to management of the airway Single shot spinal anaesthesia has become the preferred technique during the past 15 years. Recent studies have demonstrated that preeclamptic patients may experience less hypotension after spinal anaesthesia than their healthy counterparts,^{4,5} and hypotension tends to be less severe in patients with marked hypertension. In conjunction with this, authors have found less vasopressor requirements in these women as well.^{6,7,8} A modest lowering of the blood pressure has been shown to represent afterload reduction, which is in principle desirable in these patients.⁹ However, severe hypotension does occur after induction of spinal anaesthesia in some cases, which may further compromise the mother and a fetus that are already at high risk. In only one observational study has phenylephrine (P) been studied for the treatment of spinal hypotension in patients with preeclampsia.⁹ Small doses reversed hypotension and restored the systemic vascular resistance.⁹ There have been no comparisons of the maternal haemodynamic effects of the alpha agonist phenylephrine and the mixed acting alpha/beta agonist ephedrine during spinal anaesthesia in preeclampsia. The primary aim of this study is to compare the haemodynamic changes associated with the first administration of phenylephrine or ephedrine.

Patients and methods

Preeclampsia is diagnosed if the diastolic blood pressure after 20 weeks' gestational age is greater than or equal to 90 mmHg on two separate occasions at least 4 hours apart, and proteinuria of 2+ on urine dipstick in two clean midstream samples taken

at least 4 hours apart, or greater than or equal to 300 mg protein per 24 hours. Severe preeclampsia is diagnosed if the systolic blood pressure exceeds 160 mmHg and/or the diastolic blood pressure exceeds 110 mmHg, obtained on at least two separate occasions, or if the patient has symptoms of imminent eclampsia (namely severe headache, visual disturbance, epigastric pain, hyperreflexia, dizziness and fainting, or vomiting) and proteinuria on urine dipstick is 3+ or worse.

Informed written consent was taken wherever possible when the diagnosis was made after admission to hospital. In some cases, it was necessary to obtain consent closer to the time of decision to proceed to caesarean section. The study commenced after the approval of the Health Science Faculty Human Research Ethics Committee (HSFHREC) of the University of Cape Town, and was performed at the New Groote Schuur Hospital Maternity Centre.

Maternal exclusion criteria entailed: patient refusal, any contra-indication to spinal anaesthesia, body mass index greater than 40 kg/m², clinical signs of hypovolemia, abruptio placentae, placenta praevia, coagulation abnormality, thrombocytopenia (platelet count < 75x10⁹/L), pulmonary oedema, local or generalized sepsis, spinal deformity, cord prolapse, prior non-obstetric abdominal surgery, more than 2 previous caesarean sections, or patients who are HIV positive and have AIDS-defining disease at the time of recruitment. Fetal exclusion criteria: persistent fetal bradycardia or any other fetal condition contraindicating spinal anaesthesia, gestational age < 28 weeks, and twin pregnancy.

Any spinal anaesthetic that took longer than 20 minutes to perform was aborted and the patient received a general anaesthetic. The data was recorded as a failure of the technique.

Prior to being recruited to the study, the antepartum management was instituted according to the established protocol at Groote Schuur: if the patient is in established labour, an intravenous line will be inserted, and a balanced crystalloid solution administered at less than 100 mL per hour. Patients not in labour were allowed free oral fluids. Seizure prophylaxis was administered to patients with severe preeclampsia, consisting of magnesium sulphate (MgSO₄), administered as a loading dose of 4g intravenously, followed by 1g hourly intravenously. Dihydrallazine was administered intravenously as a vasodilator, for additional blood pressure control against a standardized protocol. Prior use of other agents (alphamethyldopa, morphine and dexamethasone) was recorded.

All patients received 30 ml sodium citrate orally in theatre, as well as 1g cefazolin IV prior to induction of SA. Non-invasive monitoring consisted of electrocardiograph, non-invasive blood pressure and pulse oximetry in all patients. A 20G arterial line was placed on arrival in the operating theatre, and pulse wave form analysis commenced using the LiDCO*rapid* machine, which employs a pulse power algorithm for beat by beat determination of the stroke volume. Data was recorded from 5 minutes pre-SA until 45 minutes post SA or until the end of surgery if the duration was longer than 45 minutes. Baseline mean arterial pressures were taken as the mean of two non-invasive blood pressure readings not differing by more than 10%, taken in the 5 minutes prior to induction of spinal anaesthesia, measured at rest in the left lateral position. After measurement of baseline blood pressure, the target value for administration of vasopressor was calculated.

The management of spinal anaesthesia:

All patients received 2.0 – 2.2 ml of hyperbaric 0.5% bupivacaine, with 10 µg of fentanyl, administered in the sitting position at the L3/4 interspace. After 20 seconds in the sitting position, patients were positioned supine, with 15 degrees of left lateral tilt, to minimise aortocaval compression. Block height assessed using cold sensitivity to ethyl chloride spray, and surgery commenced when a block level of T4 is achieved. All mothers received 40% oxygen by face-mask. The management of hypotension was as follows:

Twenty patients were randomised at the time of requirement for a vasopressor, to receive either 7.5 mg E or 50 µg P in response to a 20% decrease from baseline mean arterial pressure (MAP), if this was associated with an absolute value of the mean arterial pressure of less than 110 mmHg (target value). Should the MAP not be restored to the target value within 60 – 90 seconds, 7.5-15 mg E or 50-100 µg P was given. If the target was not achieved after a total of either 45 mg of ephedrine or 300 µg of phenylephrine, the alternative vasopressor was used. Should MAP at any point decrease to more than 30% below baseline, 15 mg ephedrine or 100 µg phenylephrine was given. If HR decreased to less than 55 beats per minute in association with hypotension (MAP decrease by 30% from baseline), ephedrine 10 mg was administered, followed by atropine 0.25-0.5 mg if bradycardia persisted. No patient received more than 50 mg ephedrine, since this was interpreted as tachyphylaxis. Syringes were pre-prepared by an investigator not involved with the performance of the anaesthesia, so that the anaesthetist was blinded as to the vasopressor given. The study was concluded at delivery.

Statistical analysis:

Sample size calculation for the comparison of vasopressor effects was based upon the outcomes of a previous study.¹⁰ This study, which examined peak percentage change in CO from baseline after administration of phenylephrine or ephedrine, showed a peak change following phenylephrine of – 27.8% (SD 10.7%), and a peak change following ephedrine of +16% (SD 19.5%). Assuming these changes, a sample size of 5 per group would have 90% power employing a two sided test, if statistical significance is defined at $P=0.05$. Due to uncertainty with respect to inter-patient variability, and expected variability in response to vasopressors at the lower doses used in the present study, the sample size was increased to 10 per group. For the purpose of analysing the haemodynamic response to the first dose of vasopressor, the pre-vasopressor value was taken as the mean value for the period 30 seconds before vasopressor administration. The post-vasopressor period of measurement was 150 seconds. For each of the time periods of observation, mean values were calculated for each participant. For the post-vasopressor period the mean percentage change from the mean value in the pre-vasopressor period was also calculated for each participant. Descriptive statistics were calculated for each period based on the mean values for each participant by group. All observed values for the study periods were included in the analysis, as well as for all participants randomised. The two sample t-test was used to compare the mean values between the groups and the mean percentage differences were also calculated with their 95% confidence intervals. Median smooth plots were used to graphically display the mean percentage change in CO in each group at each time point of the post-vasopressor pressure period, in combination with the profiles at the individual participant level. Similar summary median smooth plots are presented for comparison of cardiac output, mean arterial pressure, systemic vascular resistance, stroke volume and heart rate.

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Part B: Narrative literature review

Maternal cardiac output response to vasopressor during spinal anaesthesia for caesarean section in patients with severe preeclampsia

Literature sources:

The electronic database used for this narrative review was Pubmed, as well as the University of Cape Town electronic database, and the WHO website for statistical data. The following keywords were used: “preeclampsia”, “spinal hypotension”, “phenylephrine and ephedrine in pregnancy”, “maternal haemodynamics in preeclampsia”.

Of over 600 articles identified, 35 articles were included in this review. The sources were editorials, reviews, cohort studies, observational studies, meta analyses, case series and randomized controlled trials.

Introduction:

Preeclampsia is a multisystem disorder which complicates 8-12% of pregnancies, and has been established as a major contributor to maternal and perinatal morbidity.^{1,2,3} Infants of mothers with preeclampsia have a 2 fold increased risk of neonatal death.² A recent Lancet review¹ has reported that hypertensive disorders during pregnancy, are the second most common cause of maternal death, after maternal haemorrhage. In this systematic analysis, 417 databases from 115 countries generated 23 eligible studies comprising of 60799 deaths for the period 2003 and 2009. The various causes, direct and indirect, were evaluated. Haemorrhage accounted for 27.1%, hypertensive disorders 14.0% and sepsis 10.7%. It has been postulated that the initiating event in preeclampsia is reduced placental perfusion which results in placental ischaemia, eventually leading to widespread maternal vascular endothelial dysfunction. The dysfunctional endothelium results in enhanced formation of endothelin and thromboxane, increased sensitivity to angiotensin II and decreased formation of vasodilators like nitric oxide and prostacyclin. These abnormalities cause hypertension by impairing renal pressure natriuresis and increasing total peripheral resistance.^{4,5} Lisonkova et al.², in a major retrospective observational study of singleton pregnancies in preeclamptic patients, evaluated the incidence of the disease, the associated risk factors and the birth outcomes. There are two distinct subtypes of this disease, based on the timing of onset: early onset preeclampsia occurring at 34 weeks gestation or less and late onset preeclampsia occurring at 34 weeks or

more.^{2,6} The earlier the onset of the disease process, the higher the risk of life threatening complications.^{2,6} A prospective cohort study by Stergiotou et al⁷ in 100 preeclamptic patients and 100 healthy parturients, suggests that the distinct vascular adaptations in early and late preeclampsia could reflect different pathophysiologic mechanisms.^{6,7} Early onset preeclampsia is characterized by high resistance and low cardiac output (CO) while late onset disease has a lower resistance and high CO state.^{4,7,8}

Recent publications on echocardiographic changes in severe preeclampsia have shown that increased inotropy with diastolic dysfunction is common. There is a range of dysfunction, more pronounced in early onset disease, and including systolic dysfunction.^{9,10}

These patients have depressed left ventricular performance which is attributable to the high blood pressures in the preeclamptic state. The left ventricle undergoes adaptive changes due to the high afterload it is subjected to with regards to structure and function. The result is a high ventricular mass with higher end systolic and end diastolic ventricular volumes with lower ejection fractions.¹¹

Anaesthesia for caesarean section (CS) therefore poses a major challenge. Hence it is important to understand the maternal haemodynamic effects of SA, and of vasopressor therapy for spinal hypotension in this high risk group of patients.

Anaesthesia in preeclampsia

General anaesthesia:

Indications for general anaesthesia include: coagulopathy, pulmonary oedema and imminent fetal demise. Rapid sequence induction for general anaesthesia for CS carries an increased risk of maternal adverse effects, particular, the haemodynamic consequences of tracheal intubation when performing a rapid sequence induction; hypertension and tachycardia may contribute to complications such as pulmonary oedema and cerebral haemorrhage. An Enquiry into Maternal Deaths 2003-2005¹² documented two cases of intracerebral haemorrhage in preeclampsia which were attributed to the intubation response associated with direct laryngoscopy. The majority of women died from intracerebral haemorrhage.

A review by Mannur et al.¹³ commented on airway problems in preeclampsia. These patients are at risk of laryngeal oedema with subsequent failed intubation and potentially fatal loss of the airway.¹⁴

The above haemodynamic disturbances and potential airway complications mitigate against the use of general anaesthesia unless regional anaesthesia is contraindicated.

Regional anaesthesia:

A review on the role of the anaesthetist in the management of the patient with severe preeclampsia emphasized the cardinal role of regional anaesthesia. In the past, the major challenges associated with regional anaesthesia were perceived to be the risk of precipitous hypotension, induced by sympathectomy associated with epidural or SA, and the management of the hypotension employing fluids and vasopressors. Wallace et al.¹⁵ conducted a randomized controlled trial to evaluate the maternal and fetal outcomes of three anaesthetic techniques in preeclamptic parturients, namely general anaesthesia (n=26), epidural anaesthesia (n=27) and combined spinal-epidural anaesthesia. Excessive fluid therapy was avoided in response to maternal hypotension associated with neuraxial anaesthesia. Maternal hypertension was avoided in the general anaesthesia group. Short term neonatal outcome was good. The authors' conclusions were that with due care, neuraxial and general anaesthesia are acceptable for preeclamptic patients undergoing CS.

Over the past 20 years, single shot spinal has become the preferred anaesthetic technique in the absence of complications. Advantages of SA include ease of technique and rapid onset of action, making it suitable for urgent surgery, as well as the avoidance of the haemodynamic consequences of tracheal intubation. Visalyaputra et al.¹⁶, in a prospective multicenter randomized controlled trial, compared the haemodynamic effects of spinal and epidural anaesthesia for caesarean delivery in patients with severe preeclampsia patients. Five tertiary care hospitals were included and 120 patients were randomized to 2 groups of 60. Five patients in the epidural group were excluded due to inadequate block and thus had general anaesthesia. A further 8 of the epidural group and 7 of the spinal group went into spontaneous labour. Patients in the spinal group had more significantly more hypotension than in the epidural group. However, the duration of clinically significant hypotension was short in both groups (<1 min). The hypotension was usually mild, and the difference in the median lowest mean arterial blood pressure measured in the spinal group compared with that in the epidural group, was small. There were no adverse maternal or fetal outcomes related to hypotension. The conclusion was that the result of this multicenter study supported the use of spinal anaesthesia (SA) for CS in preeclamptic patients. A limitation was potential variability in patient selection and clinical practice in the several hospitals involved in the study. An editorial by

Santos¹⁷ maintained that the use of single shot spinal in stable non-coagulopathic preeclamptic patients presenting for CS, is a reasonable alternative to epidural anaesthesia, particularly in an emergency.

In the setting of SA in preeclampsia, early studies employing blood pressure monitoring have shown that the incidence of hypotension, and the requirement for vasopressors, is lower than in healthy patients during SA for CS.^{18,19}

Aya et al.¹⁸ did a prospective cohort study on a group of 60 patients; 30 normotensive and 30 severely preeclamptic patients. The primary aim of the study was to compare the incidence and severity of spinal hypotension. The study showed a two times lower incidence of hypotension, and reduced vasopressor requirements in preeclampsia. In addition, the magnitude of hypotension was less in preeclampsia. Confounding variables were between-group differences in gestational age and birth weight. A subsequent study compared hypotension in preeclamptic- and healthy women with gestational age-matched fetuses, in order to eliminate the confounding variable of differing degrees of aortocaval compression. The incidence of spinal hypotension remained lower in the preeclampsia group.

A further study by Clark et al.²⁰ involving 20 normotensive patients and 20 patients with severe preeclampsia for CS under SA, also showed less spinal hypotension and a lower vasopressor requirement in preeclampsia.

It appears that the increase in vascular responsiveness of blood vessels to pressor drugs, due to endothelial dysfunction, as well as increased levels of circulating vasoconstrictor substances in preeclampsia, serves to reduce spinal hypotension in these patients. This is discussed and highlighted in a recent editorial by Sharwood-Smith et al.²¹ Increased inotropy may also play a role in the limitation of hypotension.²²

Early studies suggested that in healthy parturients maternal CO decreases in response to SA for CS.²³ More recently, beat by beat monitoring with the LiDCO monitor has shown that in healthy patients there is an initial increase in CO due to afterload reduction, and that this has greater physiological significance than venodilatation.^{24,25,26} The major effects of SA are thus decreased systemic vascular resistance, hypotension, and a partial compensatory increase in CO due to increased heart rate and stroke volume.

Techniques for the prevention or treatment of spinal hypotension include lateral uterine displacement, intravenous prehydration or coload, lower limb wrapping, and vasopressor therapy. Although crystalloid coload or colloid preload do reduce spinal hypotension, modern therapy emphasizes early intervention with vasopressors, usually ephedrine or phenylephrine, by bolus or infusion. This is

particularly important in preeclampsia, where excessive fluids may precipitate pulmonary oedema.

The selection of a vasopressor for spinal hypotension is based upon fetal and maternal outcomes. Early studies in sheep suggested that ephedrine, a direct acting β -1- and indirect α agonist, was the most effective vasopressor in terms of uterine blood flow and fetal outcome. However placentation in humans and sheep is very different, and many recent studies in healthy parturients confirm that phenylephrine, a direct-acting alpha agonist, is the drug of choice, since pH and base excess are consistently higher in cord gases of mothers treated with phenylephrine for spinal hypotension.²⁷ In addition, ephedrine readily crosses the placenta and may cause fetal acidosis, mainly due to increased fetal metabolic rate.^{29,30}

There are only a limited number of studies examining maternal haemodynamic responses to SA. This information is thus used as the basis for the choice of vasopressor.

In a prospective study by Tihonen et al³¹, whole-body impedance cardiography was used to determine how preeclampsia modifies maternal haemodynamics during spinal anesthesia when compared to normal pregnancy. A sample size of 20 was used: 10 Normal pregnancies and 10 preeclamptic pregnancies. The main outcomes measured were Stroke index (SI), systemic vascular resistance index (SVRI), Heart rate (HR), cardiac index (CI) and mean arterial pressure (MAP). Interestingly, SI and HR were increased by a preload infusion in preeclamptic patients versus only an increase in HR in the healthy group. This may be the result of a preexisting hypovolaemic state and inadequate preload, which was rectified by administration of fluid. Spinal blockade reduced SVRI in both groups of patients, CI remained stable throughout. At delivery CI increased in both groups. The resulting increase in CI in the healthy group of patients was attributable to a rise in SI and HR, whereas in the preeclamptic group, the increase in CI was due to a rise in HR and not in SI. This may be due to left ventricular dysfunction, making these women vulnerable to pulmonary oedema.

A study employing minimally invasive CO monitoring has shown that bolus phenylephrine administered in response to spinal hypotension in healthy parturients, restores blood pressure, SVR, heart rate, stroke volume and CO to close to baseline values, and was found in healthy patients to be the more appropriate vasopressor than ephedrine, to reverse the typical haemodynamic changes induced by SA. Heart rate changes have been shown to correlate well with CO change in response to vasopressor administration.^{25,26} Further studies employing suprasternal Doppler

technology have clearly shown the dose-related reduction of maternal CO by phenylephrine.^{32,33}

The LiDCO monitor was used in one observational study of 15 patients with severe preeclampsia, to assess maternal haemodynamic changes and response to vasopressor. CO and systemic vascular resistance were derived from the measured stroke volume, heart rate and mean arterial pressure. The haemodynamic effects of phenylephrine, the response to delivery and the effects of oxytocin were also recorded. Mean arterial pressure and systemic vascular resistance decreased immediately following SA. The main haemodynamic effect of SA in these patients was a modest afterload reduction, and cardiac output was maintained. In this study spinal hypotension was treated with 50 µg phenylephrine, which resulted in restoration of blood pressure and a modest decrease in CO.³⁴

One further observational study of 6 patients, using the LiDCO monitor, described the effects of ephedrine and phenylephrine during SA for CS in severe preeclampsia and normal pregnancies. Vasopressors were used to obtund hypotension due to oxytocin. In his case series, Archer et al.³⁵ found that phenylephrine was an excellent vasopressor for restoring systemic vascular resistance and reversing the increase in cardiac output caused by neuraxial anaesthesia and oxytocin administration.

Although haemodynamic instability is less common in preeclampsia than in healthy women, spinal hypotension may be clinically important with clinical morbidity and potential mortality in some patients. There have been no randomised studies examining the use of ephedrine or phenylephrine for spinal hypotension during SA for CS in severe preeclampsia. Therefore a prospective, randomised double-blind study was undertaken to establish the maternal haemodynamic changes associated with the two vasopressors during SA for CS scheduled for worsening maternal disease, in order to determine the appropriate intervention for spinal hypotension in this high risk group of patients.

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Part C: Publication ready manuscript

Maternal cardiac output response to vasopressor therapy during spinal anaesthesia for caesarean section in severe preeclampsia

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Summary

We examined the haemodynamic effects of ephedrine and phenylephrine during spinal anaesthesia for caesarean section in 39 women with severe early onset preeclampsia. Twenty patients who developed spinal hypotension were randomised to 2 groups of 10, who received either 7.5 mg ephedrine or 50 µg phenylephrine; the primary outcome was the percentage change in cardiac index. Spinal hypotension in 20 patients was associated with an increase in mean cardiac output from baseline (mean difference 0.7 L/min, $p < 0.0001$). In response to vasopressor, the mean [SD] percentage change in cardiac index was greater, and negative, in patients receiving phenylephrine versus ephedrine (-12 [7.3] vs 2.6 [6] L/min respectively, $p = 0.0001$). Post-vasopressor mean percentage change [SD] in heart rate and systemic vascular resistance (SVR) were higher in patients receiving phenylephrine (-9.1 [3.4] vs 5.3 [12.6], $p = 0.0027$, and 22.3 [7.5] vs -1.9 [10.5]%, $p < 0.0001$ respectively). Phenylephrine effectively reverses spinal anaesthesia-induced haemodynamic changes in severe preeclampsia, if left ventricular systolic function is preserved.

Introduction

There are no studies that formally examine the haemodynamic responses to vasopressors administered for spinal hypotension during caesarean section (CS) in patients with severe preeclampsia. This study was a randomised comparison of the cardiac output response to the two most commonly used vasopressors, phenylephrine and ephedrine, administered in response to spinal hypotension.

Methods

Recent recommendations are that proteinuria is no longer an absolute requirement for the diagnosis of preeclampsia, and a new nomenclature, “preeclampsia with severe features”, has been advocated.² However, at the time of initiation of the present study, the diagnosis and management of preeclampsia was similar to that described in a previous publication.³ Preeclampsia was diagnosed if the diastolic blood pressure after 20 weeks’ gestational age is greater than or equal to 90 mmHg on two separate occasions at least 4 hours apart, and proteinuria of 2+ on urine dipstick in two clean midstream samples taken at least 4 hours apart, or greater than or equal to 300 mg protein per 24 hours. Preeclampsia was defined as severe if the systolic blood pressure exceeded 160 mmHg and/or the diastolic blood pressure exceeds 110 mmHg, obtained on at least two separate occasions, or if there are symptoms of imminent eclampsia (headache, visual disturbance, epigastric pain) and proteinuria on urine dipstick is 3+ or greater.

Patients with severe preeclampsia and a maternal indication for CS were recruited. The study was registered with the South African National Clinical Trial Register (DOH-27-1111-3887), and conducted at the New Groote Schuur Hospital Maternity Centre in Cape Town, South Africa. Informed written consent was taken at least 12 hours prior to operative delivery. Approval was obtained for the conduct of the study from the Health Sciences Faculty Human Research Ethics Committee of the University of Cape Town.

Maternal exclusion criteria were: patient refusal, any contraindication to spinal anaesthesia, active labour, body mass index greater than 40 kg/m², pulmonary oedema, umbilical cord prolapse, prior non-obstetric abdominal surgery, more than 2 previous CS, or patients who were HIV positive and had AIDS-defining disease at the time of recruitment. Fetal exclusion criteria were a non-reassuring fetal heart tracing, gestational age < 28 weeks, and multiple pregnancy. Failed spinal anaesthesia precluded data collection.

The antepartum management was according to the established protocol of Groote Schuur Hospital: during acute management, an intravenous line was inserted, and a balanced crystalloid solution administered at less than 100 mL per hour. Patients with severe disease received 4g IV magnesium sulphate (MgSO₄) as seizure prophylaxis, then 1 g hourly. The peripheral vasodilator dihydralazine was given IV to reduce systolic blood pressure to less than 160 mmHg. When stable, patients were admitted to the ward and allowed free oral fluids. They were then placed on maintenance alphamethyldopa, and nifedipine, should systolic blood pressure exceed 160 mmHg. Management was expectant until 34 weeks’ gestation, or until either the maternal or fetal condition required urgent delivery (deteriorating renal function, the development of HELLP syndrome, or a non-reassuring fetal heart tracing).

At 34 weeks' gestation induction of labour was attempted, if deemed appropriate by the attending obstetrician. In the event of a failed induction of labour, or if induction of labour was not appropriate, caesarean delivery was performed under spinal anaesthesia. Previous caesarean delivery was also an indication for elective repeat CS.

In theatre, patients were given 30 mL oral sodium citrate orally and 1g cefazolin IV prior to induction of SA. Non-invasive monitoring was then established: electrocardiograph, non-invasive blood pressure and pulse oximetry. A 20G arterial line was placed on arrival in the operating theatre, and pulse wave form analysis commenced using the LiDCO*rapid* pulse wave form monitor (LiDCO, Cambridge, UK), which employs a pulse power algorithm for beat by beat determination of stroke volume. A calibration factor is then applied, using a nomogram incorporating patient-specific characteristics.

The management of spinal anaesthesia was similar to that described in a previous publication, except for the use of colloid preload, and a slightly higher dose of spinal bupivacaine.³ Baseline mean arterial pressures was taken as the mean of two non-invasive blood pressure readings not differing by more than 10%, taken in the 5 minutes prior to induction of spinal anaesthesia, measured at rest in the left lateral position. After measurement of baseline blood pressure, the target value for administration of vasopressor was calculated. Baseline haemodynamic values (heart rate [HR], mean arterial pressure [MAP], stroke volume [SV], cardiac output [CO] were measured. Systemic vascular resistance was calculated assuming a central venous pressure of 5 mmHg. Data from each consecutive wave form were downloaded to an Excel chart (Microsoft, Redmond, WA). The patient was placed in the left lateral position, and a preload of 300 mL hydroxyethyl starch (Voluven®) was rapidly administered.

Spinal anaesthesia consisted of 2.0 – 2.2 ml of hyperbaric 0.5% bupivacaine, with 10 µg of fentanyl. Anaesthesia was performed in the sitting position at the L3/4 interspace. After 20 seconds, patients were positioned supine, with 15 degrees of left lateral tilt, to reduce aortocaval compression. Cold sensitivity to ethyl chloride spray was used to assess the block, and surgery began when a block height of T4 was reached. Patients received 40% oxygen by face-mask.

In response to hypotension:

Twenty patients were randomised to receive either ephedrine or phenylephrine at the time that a vasopressor was required. Blocked randomisation was used (randomised a block size of 2 or 4 using nquery Advisor Version 6, Statistical Solutions, Cork, Ireland). Sealed envelopes were prepared by the statistician. Syringes were pre-prepared by an investigator not involved with the performance of the anaesthesia, so that the anaesthetist was blinded

as to the vasopressor given. Patients received either 7.5 mg ephedrine or 50 µg phenylephrine in response to a 20% decrease from baseline mean arterial pressure (MAP) (=target value), if this was associated with an absolute value of the mean arterial pressure of less than 110 mmHg. If the MAP was not restored to the target value within 60 – 90 seconds, 7.5-15 mg E or 50-100 µg P was given. If the target was not achieved after a total of either 45 mg of ephedrine or 300 µg of phenylephrine, the pre-prepared alternative vasopressor could be used. Should MAP at any time decrease to more than 30% below baseline, 15 mg ephedrine or 100 µg phenylephrine was given. If heart rate (HR) decreased to less than 55 beats per minute in association with hypotension (MAP decrease by 30% from baseline), the protocol allowed for ephedrine 10 mg, followed by atropine 0.25-0.5 mg if bradycardia should persist. No patient received more than 45 mg ephedrine, since this was interpreted as tachyphylaxis. The attending anaesthesiologist was blinded as to the vasopressor administered.

All maternal medications received in the 24 hours prior to anaesthesia were noted. Severity of disease (as assessed by the degree of hypertension and the requirement for vasodilator and/or seizure prophylaxis therapy, and degree of proteinuria) was also recorded, as well as maternal side-effects, in particular nausea and vomiting. Umbilical arterial and venous blood samples were analysed shortly after delivery, and Apgar scores recorded.

Statistical analysis:

Sample size calculation for the comparison of vasopressor effects was based upon the outcomes of a previous study.⁴ This study, which examined peak percentage change in CO from baseline after administration of phenylephrine or ephedrine in healthy patients, showed a peak change following phenylephrine of – 27.8% (SD 10.7%), and a peak change following ephedrine of +16% (SD 19.5%). Assuming these changes, a sample size of 5 per group would have 90% power employing a two sided test, if statistical significance is defined at P=0.05. Due to uncertainty with respect to inter-patient variability, and expected variability in response to vasopressors at the lower doses used in the present study, the sample size was increased to 10 per group. It was envisaged that approximately 40% of patients would require vasopressor pre-delivery, hence 50 patients might require recruitment in total.

For the purpose of analysing the haemodynamic response to the first dose of vasopressor, the pre-vasopressor value was taken as the mean value for the period 30 seconds before vasopressor administration. The post-vasopressor period of measurement was 150 seconds. For each of the time periods of observation, mean values were calculated for each participant. For the post-vasopressor period the mean percentage change from the mean value in the pre-vasopressor period was also calculated for each participant. Descriptive

statistics were calculated for each period based on the mean values for each participant by group. All observed values for the study periods were included in the analysis, as well as for all participants randomised. The two sample t-test was used to compare the mean values between the groups and the mean percentage differences were also calculated with their 95% confidence intervals. Median smooth plots were used to graphically display the mean percentage change in CO in each group at each time point of the post-vasopressor pressure period, in combination with the profiles at the individual participant level. Similar summary median smooth plots are presented for comparison of cardiac output, mean arterial pressure, systemic vascular resistance, stroke volume and heart rate.

Results

Details of patient recruitment are shown in the CONSORT diagram (Figure 1). A total of 39 patients were recruited to this randomised trial from January 2011 until April 2013; 20 required vasopressor pre-delivery, and were randomised to receive either ephedrine or phenylephrine.

In the 2 groups of 10 patients randomised to receive phenylephrine or ephedrine, mean [SD] age (28 [5.5] vs 30.8 [5.6] years), weight (89 [16] vs 86 [11] kg), height (1.6 [0.04] vs 1.6 [0.09] metre), median [range] gravidity (3 [1-5] vs 2 [1-4]), parity (1 [0-3] vs 1 [0-3]), and gestational age (34 [32-36] vs 34 [31-34] weeks), were similar. All operative deliveries were for a maternal indication, mostly early onset preeclampsia reaching 34 weeks' gestation, and/or previous CS.

Median (range) block height was T3 (T2-T6) in both groups. Baseline and pre-vasopressor data is shown in Table 1. There were no differences between groups. In patients who developed spinal hypotension, mean cardiac output and heart rate had risen, and mean arterial pressure and systemic vascular resistance had decreased significantly from baseline in at the time of vasopressor administration (Table 2).

Changes in haemodynamic indices in response to vasopressor, appear in Table 3. The median (range) of ephedrine and phenylephrine required in the 150 seconds post hypotension was 15 (7.5-37.5) mg and 50 (50-150) µg respectively. The mean [SD] percentage change in cardiac index was greater, and negative, in patients receiving phenylephrine versus ephedrine (-12 [7.3] vs 2.6 [6] L/min respectively, $p=0.0001$). Figure 2 is a median smooth plot of cardiac output changes in response to the vasopressors, including individual profiles. Post-vasopressor mean percentage change (SD) in heart rate and systemic vascular resistance (SVR) were higher in patients receiving phenylephrine (-9.1 [3.4] vs 5.3 [12.6], $p=0.0027$, and 22.3 [7.5] vs -1.9 [10.5]%, $p<0.0001$ respectively). Figure 3 shows summary median smooth plots of all the haemodynamic variables.

There were no significant differences between the phenylephrine and ephedrine groups in mean [SD] umbilical arterial pH (7.28 [0.04] vs 7.28 [0.03]), base excess (-2.16 [3.05] vs -3.59 [3.47] mmol/L), or lactate (2.16 [0.65] vs 2.47 [0.55] mmol/L).

Discussion

There are limited studies examining haemodynamic responses to vasopressors during SA for CS in early onset severe preeclampsia. We found that spinal hypotension requiring vasopressor therapy was associated with a significant increase in maternal CO from pre-spinal anaesthesia values. In the doses used, the haemodynamic response to phenylephrine was significantly different to ephedrine with respect to SVR, CO and HR. Phenylephrine effectively reversed the spinal anaesthesia-induced decrease in SVR, as well as the increase in CO and heart rate. Ephedrine did not significantly change CO. The study suggests that large doses of ephedrine may be necessary to reverse hypotension (Table 3), and that phenylephrine is the first choice vasopressor in women with severe preeclampsia and preserved systolic function.

Spinal hypotension is known to be less common in severe preeclampsia, and CO has been shown to be well maintained.^{5,6} An observational study has noted the effects of phenylephrine and ephedrine boluses in 4 patients with severe preeclampsia.⁷ One other previous observational study showed the effects of a bolus of 50 µg phenylephrine on maternal cardiac output, but there was no formal comparison with ephedrine.⁶ In the present study the alpha agonist phenylephrine was found to be more effective than ephedrine in reversing the decrease in SVR associated with SA. The reversal of spinal anaesthesia-induced CO changes by phenylephrine were similar to the findings of a previous investigation in healthy parturients.⁴ Ephedrine maintained the pre-vasopressor CO by increasing heart rate.

Current guidelines for fluid management in preeclampsia state that volume expansion in untreated patients is not advised, and that fluid should be restricted to < 80 mL/hour for maintenance.

Study limitations were as follows:

Previous studies in obstetric anaesthesia have employed the LiDCO monitor, which uses the PulseCO algorithm for the generation of a nominal stroke volume, followed by calibration using a standard dose of IV lithium in each case.⁸ The LiDCO*rapid* device employs a calibration factor based upon a patient-specific nomogram. It is important to note that the device was used as a trend monitor rather than as a measure of absolute values of CO in this study. It was not possible to accurately control the preoperative fluid administration to each patient. Patients were kept nil per os overnight prior to CS or, if an IV line was in place, received < 100 mL/hour of IV fluid prior to CS.

The sample size, based upon CO changes measured in a previous study in healthy patients,² was small, but statistical power was adequate. Although a large number of patients with early onset preeclampsia are admitted every week in our Maternity Centre, > 90% receive SA for CS for a nonreassuring fetal heart tracing, in which case any delays for randomisation and placement of an intra-arterial line would be unethical; hence the study duration of 28 months.

It was difficult to estimate the bolus dose of ephedrine with an equivalent pressor response to 50 µg phenylephrine. The ratio of 150:1 (a bolus of 7.5 mg ephedrine versus 50 µg phenylephrine) was based on our usual clinical practice, and was higher than the previously described ratio of 80:1 employed using infusions of these vasopressors in healthy patients.⁹ Despite the higher dose ratio in this study, the magnitude of the effect of ephedrine on SVR was less than that of phenylephrine.

Most patients with severe preeclampsia have well preserved systolic function and cardiac output, as in our study, although diastolic dysfunction is common.^{10,11} However, pulmonary oedema may be associated with severe systolic heart failure,^{10,12} necessitating goal directed haemodynamic management in the individual case. Our results do therefore not apply to patients with severe preeclampsia and heart failure with a poorly preserved ejection fraction.

This study was not powered to detect between group differences in umbilical cord gas parameters; a further adequately powered study has been completed in this regard, using noninvasive maternal blood pressure monitoring (Dyer, unpublished data).

Conclusions

Cardiac output increased in response to SA, and a small dose of phenylephrine more effectively reversed spinal anaesthesia-induced haemodynamic changes than ephedrine. Phenylephrine is thus an effective vasopressor in the management of spinal hypotension during SA for CS, in patients with severe preeclampsia and preserved left ventricular systolic function.

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Table 1 Baseline and pre-vasopressor values in ephedrine (E) and phenylephrine (P) groups

		Group E (n=10)		Group P (n=10)	
Baseline		Mean	SD	Mean	SD
HR	Beats/min	87.0	18.3	88.6	18.0
MAP	mmHg	133.1	20.0	135.9	9.6
SYS	mmHg	188.3	22.8	193.1	15.3
DIAS	mmHg	101.6	15.1	104.8	7.6
SV	mL/beat	112.7	19.8	109.0	16.8
SVI		60.4	10.8	58.4	6.7
SVR	Dyne.sec.cm ⁻⁵	1114.5	367.4	1149.7	380.7
SVRI		2073.2	701.2	2114.6	619.1
CO	L/min	9.7	2.4	9.7	2.8
CI		5.2	1.3	5.2	1.2
Pre-vasopressor					
HR	Beats/min	97.8	22.5	97.7	17.9
MAP	mmHg	102.3	12.4	108.6	6.0
SYS	mmHg	146.2	14.6	156.9	10.2
DIAS	mmHg	81.3	11.9	85.3	4.7
SV	mL/beat	110.4	31.2	107.1	21.8
SVI		58.8	14.3	57.3	8.3
SVR	Dyne.sec.cm ⁻⁵	821.0	381.3	846.2	283.4
SVRI		1526.1	735.7	1553.8	479.9
CO	L/min	11.0	4.4	10.7	4.1
CI		5.8	2.1	5.7	1.8

HR = heart rate; MAP = mean arterial pressure; SYS = systolic blood pressure; DIAS = diastolic blood pressure; SV = stroke volume; SVI = stroke volume index; SVR = systemic vascular resistance; SVRI = systemic vascular resistance index; CO = cardiac output; CI = cardiac index; E = Ephedrine; P = Phenylephrine

Table 2: Comparison between baseline and pre-vasopressor haemodynamic values in the 20 patients who developed spinal hypotension. Abbreviations as for Table 1.

Variable	Mean	SD	Mean	SD	Mean diff	95% conf intervals		p-value
						lower	upper	
CO	9.7	2.6	10.8	4.1	1.1	0.1	2.2	0.0362
CI	5.2	1.2	5.8	1.9	0.6	0.1	1.1	0.0379
SVR	1132.0	364.6	833.6	327.2	-298.5	-359.9	-237	<0.0001
SVRI	2093.9	644.1	1539.9	604.7	-554.0	-662.0	-446.0	<0.0001
SYS	190.7	19.1	151.5	13.4	-39.2	-46.4	-32.0	<0.0001
MAP	134.5	15.3	105.5	10.0	-29.0	-33.6	-24.5	<0.0001
DIA	103.2	11.7	83.3	9.1	-19.9	-23.3	-16.5	<0.0001
SV	110.9	18.0	108.7	26.3	-2.1	-10.8	6.6	0.6173
SVI	59.4	8.8	58.0	11.4	-1.4	-5.9	3.2	0.5302
HR	87.8	17.7	97.7	19.8	10.0	6.3	13.7	<0.0001

			Group E (n=10)		Group P (n=10)		Difference	95% CI		p-value
			Mean	SD	Mean	SD		Lower Limit	Upper Limit	
HR										
	absolute	Beats/min	101.2	17.8	88.8	16.3	12.3	-3.7	28.4	0.1237
	Percent change	%	5.3	12.6	-9.1	3.4	14.4	5.7	23.1	0.0027
MAP										
	absolute	mmHg	102.6	16.1	115.1	11.2	-12.5	-25.5	0.5	0.0590
	Percent change	%	0.5	13.1	5.9	7.8	-5.4	-15.6	4.7	0.2764
SYS										
	absolute	mmHg	146.4	16.9	161.0	16.8	-14.5	-30.4	1.3	0.0701
	Percent change	%	0.7	12.5	2.7	9.3	-1.9	-12.3	8.4	0.6917
DIAS										
	absolute	mmHg	82.2	13.2	90.9	6.9	-8.6	-18.5	1.3	0.0837
	Percent change	%	1.6	12.2	6.5	5.8	-4.9	-13.9	4.1	0.2686
SV										
	absolute	mL/beat	108.6	31.0	103.5	20.2	5.0	-19.6	29.6	0.6715
	Percent change	%	-1.5	10.6	-3.0	9.2	1.5	-7.8	10.8	0.7402
SVI										
	absolute		57.9	14.5	55.3	8.0	2.6	-8.4	13.6	0.6284
SVR										
	absolute	Dyne.sec.cm ⁻⁵	813.8	383.7	1031.8	342.4	-218.0	-559.7	123.7	0.1968
	Percent change	%	-1.9	10.5	22.3	7.5	-24.2	-32.7	-15.6	<0.0001
SVRI										
	absolute		1507.7	724.5	1888.9	552.5	-381.1	-986.4	224.2	0.2025
CO										
	absolute	L/min	11.1	4.3	9.3	3.2	1.8	-1.7	5.4	0.2910
	Percent change	%	2.6	6.0	-12.0	7.3	14.6	8.3	20.8	0.0001
CI										
	absolute		5.9	2.0	4.9	1.3	1.0	-0.6	2.6	0.2160

Table 3 Post-vasopressor haemodynamic changes. Abbreviations as for Table 1.

Figure 1: Consort Flow Diagram

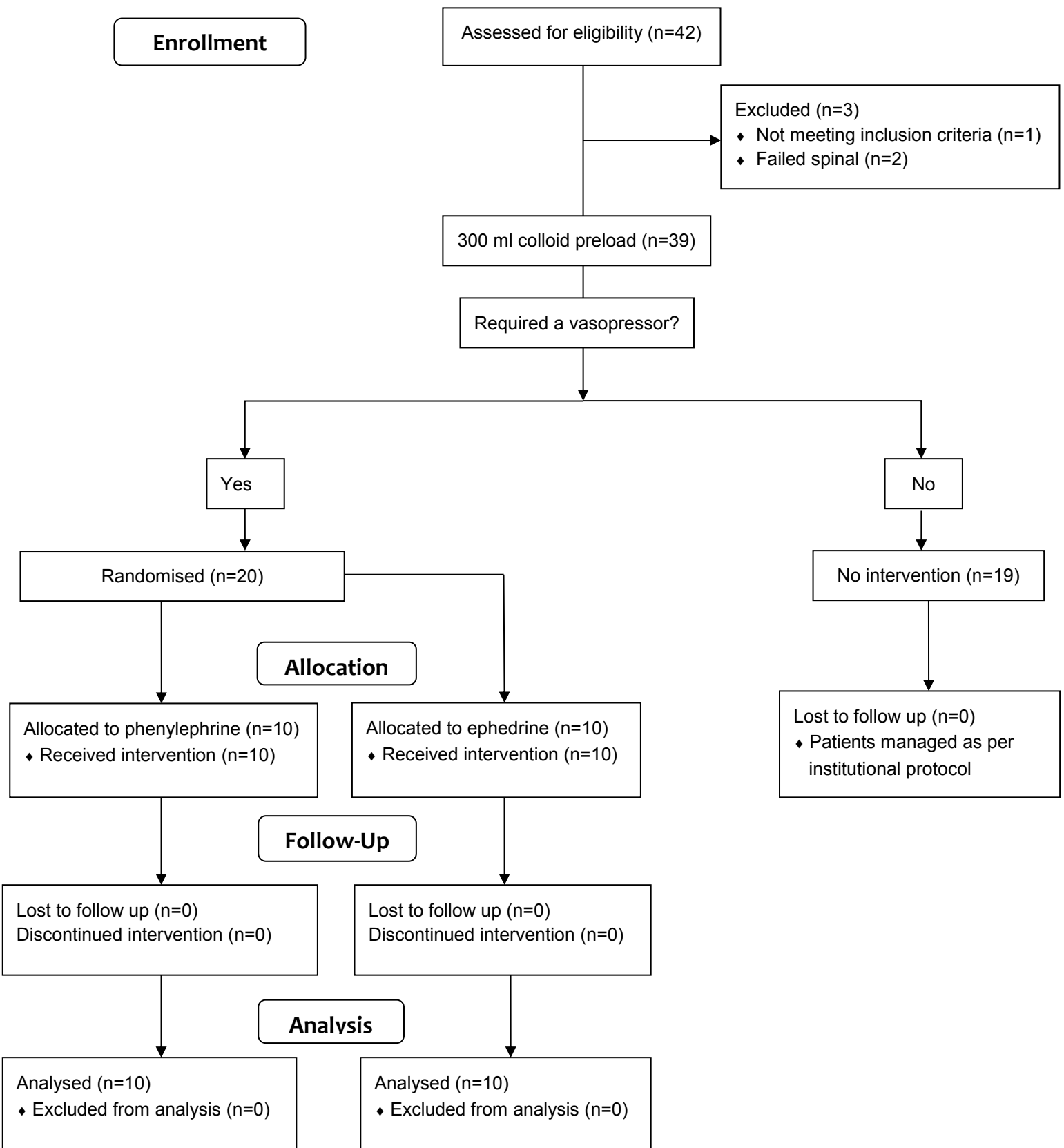


Figure 2: Median percentage change in cardiac output over 150 s after vasopressor administration. Dotted line represents mean baseline pre-spinal anaesthesia cardiac output relative to the pre-vasopressor value.

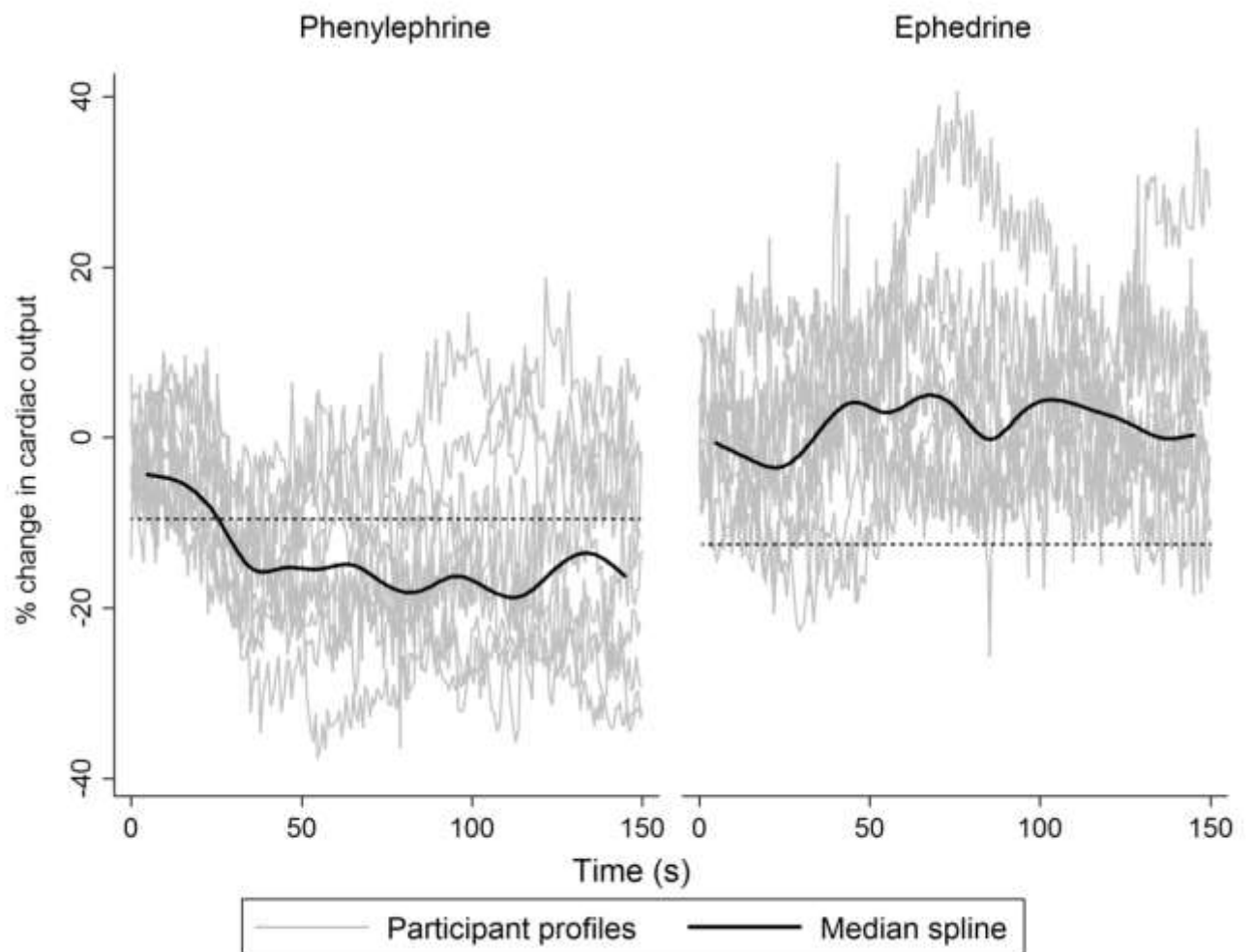
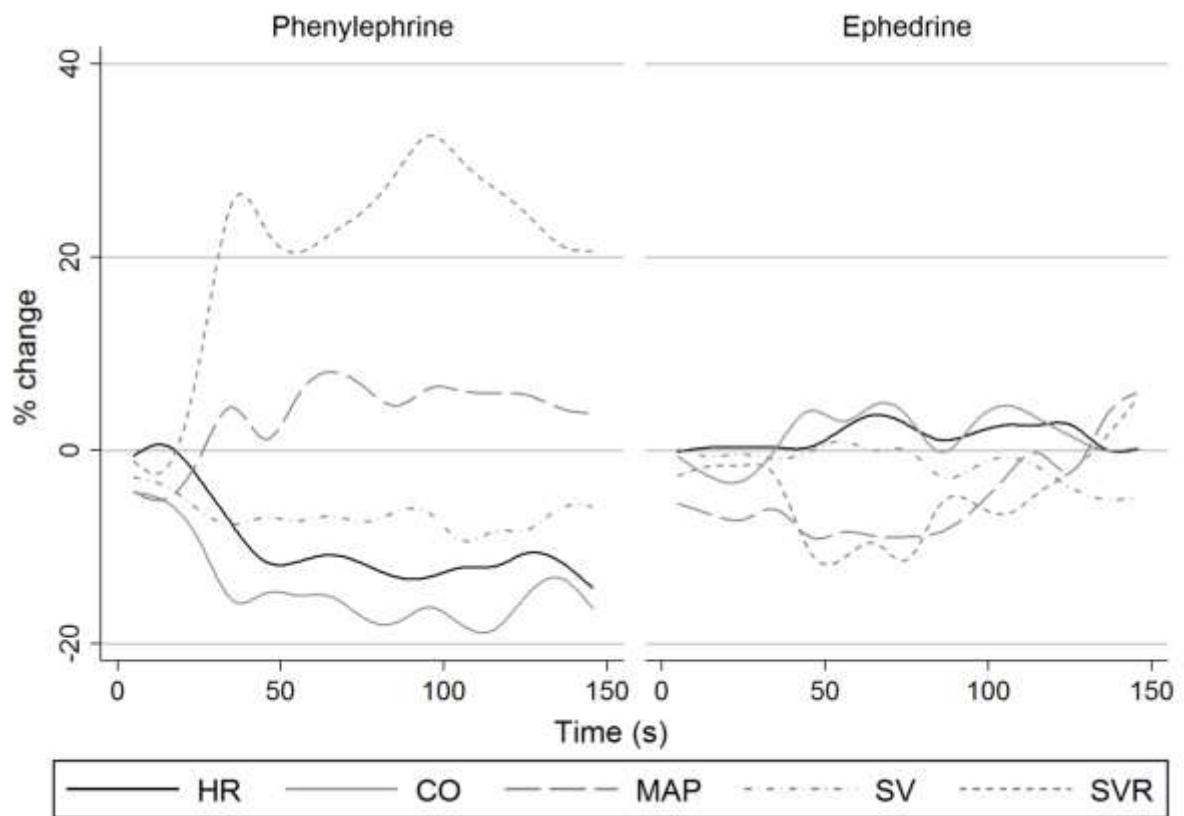


Figure 3 Median percentage change in haemodynamic variables over 150 s after administration of phenylephrine or ephedrine. HR = heart rate; CO = cardiac output; MAP = mean arterial pressure; SV = stroke volume; SVR = systemic vascular resistance.



Consent Form for LiDCO*rapid* study

A spinal anaesthetic is the method most commonly used for delivery of babies at caesarean section in mothers with your condition, as this is thought to be the safest method overall.

The doctors performing your anaesthetic would like to study the changes that happen to your heart and circulation after the spinal injection has been performed. The doctors will also study the effects of medications given into a vein if your blood pressure should drop during the anaesthetic. In addition, your baby's wellbeing after delivery will be carefully assessed. We are also studying the effects on your blood pressure and performance of your heart of different ways of giving a medication called oxytocin. This is routinely given in the mother's drip after the delivery of the baby, to encourage her womb to contract well to loosen the afterbirth and prevent major bleeding after the delivery.

These measurements will assist doctors in the future to find the best way to look after patients with preeclampsia who need a Caesarean section under spinal anaesthesia. After your baby is born, your recovery from the anaesthetic will also be recorded.

A machine (LiDCO*rapid*) will measure the changes in your heart and circulation without any discomfort or harm to you or your baby. An arterial line, which looks a lot like a drip but which is placed into the artery at your wrist, rather than into a vein like a normal drip, will be inserted after the skin over your wrist has been numbed with a small injection. The arterial line will be used by the anaesthetist to measure your blood pressure with every heartbeat, and it also allows other measurements of how your heart is working to be made painlessly for the purposes of our trial. Completely healthy mothers do not get an arterial line if they are having a caesarean section, but in mothers with severe pre-eclampsia an arterial line helps the anaesthetist to look after mother and baby better as it allows the anaesthetist to pick up and treat any blood pressure changes very quickly.

Should you agree to enter the study, then if and when your blood pressure drops, you will be randomised by opening a sealed envelope to receive one of two different well known and accepted medicines from the doctor to treat the drop in your blood pressure, in order to find out which one is the most effective, and to measure the effect on your baby.

You may withdraw from the study at any time, and should you decide not to enter the study or to withdraw, your treatment will be of the same high quality that you would receive if you entered or remained part of the study. Should you at any stage withdraw from the study, the

doctors will continue your management in the same way as if you did not have the LiDCO monitor, and use the medicines to treat your blood pressure as they believe best.

I,, hereby consent to the use of the LiDCO™ noninvasive cardiac output machine during my spinal anaesthetic, and to random treatment with one of two medicines if my blood pressure drops, as explained to me by doctor.....

Signed:

Witnessed: (1).....

(2).....

At:Date.....



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03 November 2014

HREC/REF: 786/2014

Prof R Dyer
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Dear Prof Dyer

Project Title: MATERNAL CARDIAC OUTPUT RESPONSE TO VASOPRESSOR THERAPY DURING SPINAL ANAESTHESIA FOR CAESAREAN SECTION IN SEVERE PREECLAMPSIA (MMeD-candidate- Dr A Daniels)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for approval.

It is a pleasure to inform you that the HREC has **formally approved** the above mentioned study.

Approval is granted for one year until the 30 November 2015.

Please submit a progress form, using the standardised Annual Report Form, if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

We acknowledge that the following student:-Dr Abigail Daniels is also involved in this project.

Please note that the on-going ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.

Hrec/ref:786/2014

Author guidelines: Anaesthesia

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Dr A Klein

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Anaesthesia has the following regular sections: Editorials, Original Articles, Reviews and Correspondence. Case Reports, Historical Articles or Special Articles may also be included. Editorials are often commissioned but authors are encouraged to contact the Editor-in-Chief if they wish to discuss potential topics. Authors seeking to submit official Clinical Guidelines, Consensus Statements, etc. should refer to specific guidance [here](#).

Editorials

Most editorials are commissioned by the editorial team, but some unsolicited editorials are accepted. Our editorials are primarily opinion pieces, although they should be backed up by evidence where available. The word count is usually around 2000 words excluding references. A figure or table (or even more than one) may be included, and most editorials are written by one or two authors; more than two would be unusual (but not unheard of).

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Anaesthesia welcomes both narrative and systematic reviews of potential interest to our readers. Even a narrative review should be a structured assessment of the literature, and should include a description of how articles have been selected, and if appropriate a full search strategy. It would also need some analysis and comment, not just a listing of the literature and reporting the results. It should also include an analysis of the quality of the literature. It would usually be around 4000-5000 words of text, excluding references.

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results. Heterogeneity should be explored by consideration of individual studies, by appropriate sensitivity analysis, or by meta-regression if the number of included studies allows. For more information, please see Smith AF, Carlisle J. Reviews, systematic reviews and *Anaesthesia*. *Anaesthesia* 2015; 70: 644-50.

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The Summary should follow the sequence of the main body of the text, i.e. introduction, methods, results, discussion, but should not be structured. It should briefly state the purpose of the study or investigation; basic procedures; important results (giving numbers studied, values for results with p values) including relevant findings from Results, Tables and Figures; and principal conclusions.

Use the same sequence when presenting the methods and results as in the main body of the text, always mention the groups in the same order, and ensure that the numbers in the Summary exactly match those in the main body; it may be preferable to write the summary after having finished writing the main paper, in order to ensure that these features match.

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Introduction

The Introduction should give a concise account of the subject's background. Previously published work should only be quoted if it has a direct bearing on the present study. The Introduction should clearly and explicitly state the aims of the project.

Methods

A statement confirming Local Research Ethics Committee approval and written informed consent should be at the beginning of this section (see Ethical Considerations, below). The Methods section must describe in sufficient detail the techniques and processes used so that the investigation can be interpreted and repeated by readers. Any modification of previously published methods should be described and the appropriate reference given. If the methods are commonly used, only a reference to the original source is required. If special equipment is used, then the manufacturer's details (including town and country) should be given in parentheses. Drugs should be identified by their recommended international non-proprietary names (NB adrenaline and noradrenaline are used in preference to epinephrine and norepinephrine). Label groups in a way that is easy to follow; thus 'propofol group' and 'thiopental group' instead of 'Group P' and 'Group T'. (Occasionally, abbreviated group titles may be better, e.g. 'Group BLAB' instead of 'bupivacaine-lidocaine-adrenaline-bicarbonate group'). Remember to include inclusion/exclusion criteria and a justification of sample size. For randomised controlled trials, sufficient detail should be given on the following to allow readers to properly judge the risk of bias in the study: random sequence generation, allocation concealment, blinding (of patients, investigators, clinical staff, observers/assessors as appropriate) and handling of dropouts/withdrawals (intention to treat principle). Selective reporting bias will be assessed by comparison of the report with its protocol/trial registry entry (see above). The statistical methods used to investigate data should be given at the end of the Methods section (see below).

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Express results as mean (SD), median (IQR [range]) or number (proportion) as appropriate. Results (including actual p values) must be presented for all measurements detailed in the Methods section, and in the same order. Results should not be repeated unnecessarily. For example, if a graph is used, do not also present the same information in the text or in a Table. Results should not be given to an unwarranted number of decimal places and 95% confidence intervals should be used where possible (see Statistics, below).

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Report actual p values, rather than ranges or limits (e.g. $p=0.032$, rather than $p<0.05$).

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The Discussion should not merely recapitulate the results but should present their interpretation against a background of existing knowledge. Any conclusions must be warranted by the results. In general, avoid a paragraph headed 'Conclusions' that merely repeats a summary of the results. Also avoid ending with 'further work is needed' (it almost always is) unless you have specific areas of research to suggest.

Acknowledgments

The authors should acknowledge those who have made substantial contributions to the study or preparation of the manuscript but whose contributions do not fulfil the requirements for authorship (see above). For Case Reports, a statement 'Published with the written consent of the patient(s)' should be included. The trial registration site and number should be included in this section.

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For children: age, weight, height and BMI should be expressed as median (IQR [range]).

The study groups should form the columns rather than the rows. If statistical comparisons are being made, a separate column with exact p values should appear.

Example:

Table 2 Characteristics of intrathecal blocks with levobupivacaine or bupivacaine in patients undergoing knee replacement. Values are mean (SD), median (IQR [range]) or number (proportion).

	Levobupivacaine (n=40)	Bupivacaine (n=40)	p value
Time to T10; min	7.8 (1.9)	6.4 (2.0)	0.002
Time to peak sensory block; min	26.4 (7.2)	21.8 (5.7)	0.002
Time to two-segment regression; min	80.3 (9.9)	78.3 (10.9)	0.41
Time to maximum motor block; min	19.1 (5.4)	9.5 (4.2)	0.0001
Time to motor block regression; min	145.6 (18.5)	139.9 (22.4)	0.22
Time to L5; min	245.5 (30.1)	239.7 (32.9)	0.41
VAS for discomfort/pain during surgery*	7 (6-8 [5-9])	6 (5-7 [4-8])	0.011
Supplementation with fentanyl	8 (20%)	6 (15%)	0.77

*VAS; visual analogue score

Figures

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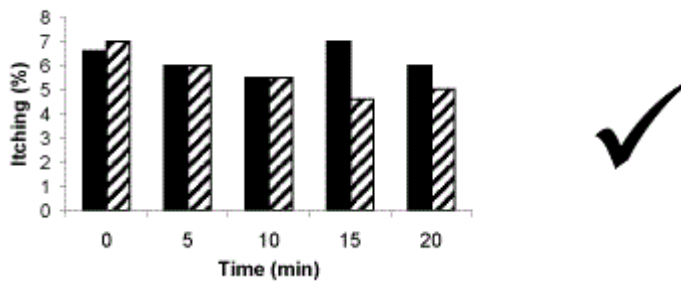


Figure 1 Itching after surgery in patients receiving saline () or chlorphenamine (). No significant difference between groups.

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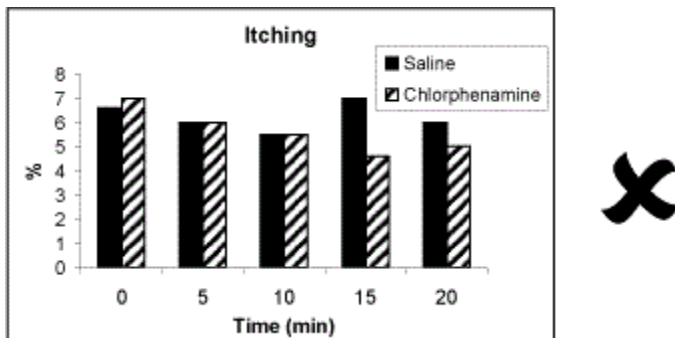


Figure 1 Itching after surgery.

See notes below for ethical considerations relating to photographs.

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Similarly, patients are not induced – anaesthesia is – or put on ventilators. Correct terms are tracheal (not endotracheal) tube and neuromuscular blocking drugs (not muscle relaxants). Please refer to recent issues of the Journal for preferred wording/spelling, e.g. “manikin” is preferred to “mannequin”, and “supraglottic airway device” is preferred to “extraglottic airway device”.

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Use the format mg.kg⁻¹ not mg/kg for all units. Use SI units throughout the text except for vascular pressure measurements (mmHg or cmH₂O) and haemoglobin concentration (g.l⁻¹). Litres are indicated by lower case 'l' not upper 'L'. Use the 24-hour clock for times.

Ethical considerations

Whatever their other merits, manuscripts will only be considered for publication in *Anaesthesia* if they adhere to the highest ethical standards. These are detailed in two editorials published in the journal, that are available [here](#) and [here](#) and which potential authors are strongly advised to consult.

The Editorial Board takes all cases of possible publication misconduct seriously and will investigate these according to the recommendations of the [Committee on Publication Ethics \(COPE\)](#). Further guidance can be found in our [Editorial Policies](#).

All clinical trials that prospectively assign human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome should be registered before the time of first recruitment. There are several public registries now available which meet the requirements of the ICMJE and these are listed on the [WHO International Clinical Trials Registry Platform \(ICTRP\)](#). The registry, registration number and date of registration must be stated in the *Acknowledgements* section of the manuscript. This should have been done before patient recruitment commenced. Reports of original research that were not registered before the study was carried out should include separate submission of the original protocol for the study. If the submitted report differs from the protocol, an explanation of the reason for this should be provided. Authors should be willing and able to submit their raw study data to the journal, if requested, after submission.

Anaesthesia supports and encourages the use of the [EQUATOR \(Enhancing the QUALity and Transparency Of health Research\) Network guidelines](#) to ensure the transparent and accurate reporting of research studies. The authors of clinical intervention studies are advised to review the [CONSORT statement](#) regarding the reporting of randomised trials prior to manuscript submission.

We strongly encourage authors to register systematic review protocols on a similar database (for instance, PROSPERO <http://www.crd.york.ac.uk/PROSPERO/>).

All clinical trials should be conducted in accordance with the ethical principles as set out in the Declaration of Helsinki. In brief, the minimum ethical standards for *Anaesthesia* include:

- Approval by a Research Ethics Committee (REC) or equivalent Institutional Review Board (IRB) must be obtained prospectively for all studies on human subjects, including studies in which participants' skills are tested using manikins. Some studies involving audit and epidemiological surveys, assessments of medical equipment or analysis of previously collected, non-identifiable information from a database may be exempt from this stricture if participants are appropriately protected against coercion and there is due regard to confidentiality. Publication of the results, however, would usually still require informed consent and assurances regarding confidentiality (including approval by the [Caldicott Guardian](#) or equivalent for patient data and the relevant Research and

Development department), even if the REC/IRB has indicated that formal submission is unnecessary.

- While an essential preliminary step, REC/IRB approval does not guarantee that the ethical standards of a study will meet the requirements of the Editorial Board of Anaesthesia. If authors have any concerns that ethical issues might compromise publication, they are invited to contact the Editor-in-Chief before embarking on the study.
- The Editorial Board supports the view of the [ICH Harmonised Tripartite Guideline for Good Clinical Practice](#) that full prospective written informed consent should be obtained from all subjects of clinical trials, including participants in manikin studies (see above). This would normally comprise provision of written information to potential research participants, allowance of adequate time for them to consider their involvement and ask questions, and the use of specific consent forms (for the study, not just for routine surgery/anaesthesia) that should be signed by the participants to indicate their consent and then stored in case they require examination later.
- Submission of a case report requires the written consent of the subject to publication, using a specific [form](#). Please do not submit this document together with your manuscript but note that authors may be asked to provide the signed form as evidence, should a complaint result in a subsequent investigation. While the Editorial Board recognises that it might not always be possible to seek such consent (or the assent of the next-of-kin if the patient has died), the onus will be on the authors to demonstrate that this exception applies in their case. Please state in an Acknowledgement at the end of the text: 'Published with the written consent of the patient(s)' or similar, as appropriate.
- Studies of novel treatments, in particular drug studies where the agent used is given via unlicensed routes (especially neuraxial or perineural), may have received approval from the REC/IRB, but the Editorial Board is likely to reject such studies if it considers that the risks posed outweigh the potential benefits. Such a conclusion is more likely to be reached if the drug in question is not widely used in routine practice (as evidenced by inclusion in standard textbooks), if the study participants are especially vulnerable (e.g. children, women in labour), if there are questions over consent, or if only modest improvements in outcome are expected where other, well established methods already exist.
- Animal studies will only be considered for publication if they have ethical and governmental approval, and have been conducted under appropriate standards of care. Researchers will be expected to follow the [ARRIVE guidelines](#) for experimentation in animal research.

Statistics

It is difficult to provide generic guidance on statistics, since statistics are designed to test a hypothesis in a quantitative way and hypotheses differ across studies. Nevertheless, the following guidelines may help authors present their work in a better and more rigorous way that avoids common statistical errors that frequently lead to rejection. This should not be regarded as an exhaustive list and, of course, the Editorial Board and reviewers of manuscripts may ask authors for revisions that are not detailed here. However, adherence to these guidelines in a paper that is otherwise acceptable will provide authors with a good footing.

Methods

Randomisation methods should be made explicit (e.g. coin toss, random numbers, etc.). Please describe if stratification of the allocation system in a randomised controlled trial is performed (e.g. by age or recruiting centre) or block (permuted sequence or otherwise). For instance, most anaesthetic RCTs have exactly the same number of patients in each group

but don't mention any blocking method (which would include putting equal numbers of folded pieces of paper for each group in an urn). Blinding must be as good as possible within constraints of clinical practice.

Where there are several outcomes to be reported, the most important (primary) outcome should be clearly stated, along with any secondary outcomes. Beware of reporting as 'significant' or 'important' a positive result of a secondary outcome, when the study was in fact powered (sample sized) to a different primary outcome.

Power analysis

Some justification of sample size is always necessary for all observational studies, randomised or non-randomised controlled trials, or other types of study. Justification may be quantitative or qualitative (e.g. a 'convenience sample'), although the latter may be regarded as weaker than the former. Details provided (for continuous variables) should include the power level; the significance level at which a result is sought; and the expected control and study group proportions or mean and pooled SD, in order to allow reviewers and readers to follow the calculation. The method used to justify power should be referenced and enough detail provided, so that the calculation can be repeated by readers. Conventionally, the power of study should be at least 80% but where different should be stated and justified. The 'clinically important difference' that the study is designed to detect should indeed be clinically relevant. Beware of setting an unreasonably large 'clinically important difference' to justify small sample size, as reviewers will recognise this is done simply to facilitate a small study.

General rules:

- Use mean (SD) unless data are discrete (e.g. Apgar scores, sedation scores) or grossly non-normally distributed: use median (IQR [range]) or you are interested in the 'true' value for the population (use SEM).
- Visual analogue scores (VAS) for pain may be treated as continuous data and be subjected to parametric tests as long as the sample size is large (> 50) and the data appear normally distributed. VAS for other modalities (nausea, drowsiness) have not been so extensively validated and are best treated as ordinal data.
- Scales of measurement can be problematic (e.g. Cormack-Lehane scale, VAS, etc.) because a value of say 2 on the scale does not imply something twice the value of 1, etc. So they cannot logically be regarded as linear, continuous scales. It is safer to regard them as ordinal scales. However, for some scales such as VAS for pain it appears established norm that this may be regarded as continuous, especially for large sample sizes (e.g. >50).

Inferential statistics

- Use simple statistical tests where possible.
- Avoid multiple comparisons, or correct for them if used.
- Reference unusual tests; and assume that the more unusual the test used, the more likely will a specialist statistical referee review the paper.
- Include details of any computer package/version used.
- When looking for relationship between variables, use correlation to describe a simple descriptive association between two variables.
- Use regression to describe a quantitative relationship between two or more variables, especially where one is predictive and other(s) dependent. Non-linear regression may be appropriate. Regression methods yield a formula to relate the variables being described.
- Use the Bland-Altman method to describe the performance of two different methods used in measurement, analysis or diagnosis.

Conclusions

All conclusions should be warranted by the results and not extend beyond the confines of the study conditions. A negative result does not mean that there is definitely no difference (confidence in the conclusion is dependent upon the power of the study), and a positive result does not mean that there definitely is a difference (confidence in the conclusion is dependent upon the alpha error).

