A randomised comparison of bolus phenylephrine and ephedrine for the management of spinal hypotension in patients with severe preeclampsia and a non-reassuring fetal heart rate trace

written by

Dr. Samantha Adams
Student no: ADMSAM005

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Supervisor: Prof. Robert A. Dyer, Department of Anaesthesia and Perioperative Medicine
University of Cape Town

DECLARATION

I, *Dr. Samantha Adams*, hereby declare that the work on which this dissertation / thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree to this or any other university.

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List of Abbreviations:

CD	Caesarean delivery
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
MAP	Mean arterial pressure
SVR	Systemic vascular resistance
HR	Heart rate
SV	Stroke volume
CO	Cardiac output
IUGR	Intra-uterine growth restriction
SFlt-1	Soluble fms-like tyrosine kinase-1
sEng	Soluble endoglin
VEGF	Vascular endothelial growth factor
PlGF	Placental growth factor
TGF-b	Transforming growth factor- beta
NRFHRT	Non-reassuring fetal heart rate trace
SD	Standard deviation
IQR	Interquartile range
CI	Confidence interval
ASA	American Society of Anesthesiologists
BE	Base excess
UA	Umbilical arterial
UV	Umbilical venous
UA/UV	Ratio of umbilical arterial to venous
PO_2	Partial pressure of oxygen
PCO_2	Partial pressure of carbon dioxide
(A-V) PCO_2	Arteriovenous PCO_2 difference
RDBT	Randomized double blinded trial
aOR	Adjusted odds ratio

PART A: STUDY PROTOCOL

As approved by the Departmental Research Committee, the Human Research Ethics Committee, and the Professional Masters Committee of the University of Cape Town.

Introduction

Hypotension remains a common clinical problem after induction of spinal anaesthesia for caesarean delivery.[1] Despite multiple techniques for preventing spinal anaesthesia-induced hypotension, including fluid preloading, left uterine displacement and administration of vasoactive drugs, no consistently successful method for prevention and treatment has been described. Hypotension results in significant morbidity (nausea and vomiting in the mother; fetal and neonatal metabolic acidosis). In terms of prevention and treatment, ephedrine has traditionally been the vasopressor of choice. This preference was based on animal studies which showed that ephedrine maintained cardiac output and uterine blood flow while direct acting vasoconstrictors (such as phenylephrine) decreased uteroplacental perfusion. However, animal studies cannot necessarily always be applied to humans and recent clinical trials have demonstrated that phenylephrine has at least similar efficacy to ephedrine for preventing and treating spinal hypotension and in addition, it is associated with an improved fetal acid base status. [2-4] The majority of these trials have been performed in healthy parturients undergoing elective caesarean delivery.

Preeclampsia complicates approximately 5% of pregnancies and is a significant cause of maternal and fetal morbidity and mortality.
Maternal and fetal death from preeclampsia is a significant risk, and sequelae of the disease include placental abruption, intracranial haemorrhage, cardiac failure, and multi-organ failure in the mother and intra-uterine growth restriction and preterm delivery of the fetus. Preeclampsia is a pregnancy-specific syndrome which occurs after the 20th week of gestation. Criteria for diagnosis of severe preeclampsia include an increased blood pressure (defined as systolic blood pressure >160 mmHg or diastolic blood pressure >110 mmHg in a woman previously normotensive) accompanied by proteinuria (urine dipstix 3+ or worse).

Many preeclamptic patients require caesarian delivery of the infant. These patients often have uteroplacental insufficiency. Neuraxial anaesthesia is preferred for caesarean delivery, due to problems related to management of the airway. 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,[5;6] and hypotension tends to be less severe in patients with marked hypertension. A modest lowering of the blood pressure has been shown to represent afterload reduction, which is in principle desirable in these patients.[7] However, severe hypotension does occur after spinal anaesthesia in some cases, and this may further compromise a fetus already at high risk. In only one observational study has phenylephrine been studied for the treatment of spinal hypotension in patients with preeclampsia. Small doses reversed hypotension and restored the systemic vascular resistance.[7] Thus, the primary aim of our study is to compare the use of bolus ephedrine and phenylephrine for the treatment of spinal hypotension in preeclamptic patients with a non-reassuring fetal heart trace, undergoing caesarean delivery. The primary outcome variable in the study will be umbilical arterial base deficit.

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 dipstix in two clean midstream samples taken at least 4 hours apart, or greater than or equal to 300 mg protein per 24 hours. Preeclampsia is regarded 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 the patient has symptoms of imminent eclampsia (namely severe headache, visual disturbance, epigastric pain, hyperreflexia, dizziness and fainting, or vomiting) and proteinuria on urine dipstix is 3+ or worse.

Informed written consent will be taken wherever possible when the diagnosis is made after admission to hospital. In some cases, it may be necessary to obtain consent closer to the time of decision to proceed to caesarian delivery. The study will commence after the approval of the Health Science Faculty Human Research Ethics Committee (HSFHREC) of the University of Cape Town, and will be performed at the New Groote Schuur Hospital Maternity Centre. One hundred and sixty patients with severe preeclampsia requiring urgent caesarean delivery under spinal anaesthesia, will be recruited into this randomised trial, which will examine the effects of bolus ephedrine or

phenylephrine administered in response to spinal hypotension, on umbilical arterial base deficit.

Maternal exclusion criteria will be: patient refusal, any contra-indication to spinal anaesthesia, body mass index greater than 40 kg/m^2, clinical signs of hypovolaemia, abruptio placentae, placenta praevia, coagulation abnormality, thrombocytopaenia (platelet count < $75x10^9$/L), pulmonary oedema, local or generalized sepsis, spinal deformity, cord prolapse, prior non-obstetric abdominal surgery, more than 2 previous caesarean deliveries, or patients who are HIV positive and have AIDS-defining disease at the time of recruitment. Fetal exclusion criteria will be persistent fetal bradycardia or any other fetal condition contraindicating spinal anaesthesia, gestational age < 28 weeks, estimated fetal weight < 900 g, and twin pregnancy.

Should any spinal anaesthetic take longer than 20 minutes to perform, the patient will receive general anaesthesia, and the data recorded as a failure of the technique.

Prior to being recruited to the study, the antepartum management will be according to the established protocol of our institution: if the patient is in established labour, an intravenous line will be inserted, and a balanced crystalloid solution administered at less than 120 mL per hour. Patients not in labour will be allowed free oral fluids. Seizure prophylaxis will be administered to patients with severe preeclampsia, consisting of magnesium sulphate ($MgSO_4$), administered as a loading dose of 4g intravenously, followed by 1g hourly intravenously. Dihydrallazine will be administered intravenously as a vasodilator, for additional blood pressure control against a standardized protocol. Prior use of other agents (alphamethyldopa, morphine and dexamethasone) will be recorded.

When a decision is made to proceed to caesarean delivery, the patient will be placed in the left lateral position before transfer to theatre, and will receive 40% oxygen by face-mask.

All patients will receive 30 ml sodium citrate orally in theatre, as well as 1 g cefazolin IV prior to induction of spinal anaesthesia. Monitoring will consist of electrocardiograph, non-invasive blood pressure and pulse oximetry in all patients. Baseline mean arterial pressures will be recorded 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 will be calculated. Thereafter a preload of 300 mL hydroxyethyl starch (Voluven ®) will be rapidly administered. Haemodynamic data will be recorded every minute after spinal

anaesthesia until 45 minutes thereafter or until the end of surgery if the duration is longer than 45 minutes.

The management of spinal anaesthesia will be as follows:
All patients will receive 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 in the absence of uterine contractions. After 20 seconds in the sitting position, patients will be positioned supine, with 15 degrees of left lateral tilt, to minimise aortocaval compression. Block height will be assessed using cold sensitivity to ethyl chloride spray, and surgery will commence when a block level of T4 is achieved. All mothers will receive 40% oxygen by face-mask. The management of hypotension will be as follows:

Patients will be randomised by sealed envelope to receive either 7.5 mg ephedrine or 50 µg phenylephrine in response to a 20% decrease from baseline mean arterial pressure (MAP), if this is associated with an absolute value of the MAP 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 ephedrine or 50-100 µg phenylephrine will be given. If the target is not achieved after a total of either 45 mg of ephedrine or 300 µg of phenylephrine, the alternative vasopressor may be used. Should MAP at any point decrease to more than 30% below baseline, 15 mg ephedrine or 100 µg phenylephrine may be given. If HR decreases to less than 55 beats per minute in association with hypotension (MAP decrease by 30% from baseline), ephedrine 10 mg will be administered, followed by atropine 0.25-0.5 mg if bradycardia persists. No patient will receive more than 50 mg ephedrine, since this will be interpreted as tachyphylaxis. Syringes will be pre-prepared by an investigator not involved with the performance of the anaesthesia, so that the anaesthetist will be blinded as to the vasopressor given. Randomisation will be performed at the time of requirement of a vasopressor. Blocked randomisation will be used (randomised block sizes of 4, 6 or 8 using nquery Advisor Version 6, Statistical Solutions, Cork, Ireland). Sealed envelopes will be prepared by the statistician.

Twenty seconds after delivery, oxytocin 3.0 IU in 3 mL saline, will be administered over a period of 60 seconds.

Umbilical arterial and venous blood samples will be collected from a segment of double-clamped umbilical cord shortly after delivery and arterial and venous blood gas parameters will be determined.

After delivery, phenylephrine 50 -100 µg or ephedrine 7.5 – 15 mg will be administered in boluses to maintain MAP above 90 mmHg.

Clinically relevant time intervals will be recorded:

a) Time from arrival in theatre until induction of anaesthesia
b) Time to T4 sensory block level
c) Induction to skin incision time
d) Induction to uterine incision time
e) Uterine incision to delivery time
f) Skin incision to closure time
g) Decision – to - delivery time

All maternal medication received in the 24 hours prior to anaesthesia will be carefully 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) and presence or absence of labour will also be recorded. Maternal side-effects, in particular nausea and vomiting, will be noted.

Neonatal outcome will be assessed by a paediatrician dedicated to the study, and blinded to the method of anaesthesia. Assessment criteria will be as follows:

The primary outcome variable will be umbilical arterial base deficit. Secondary outcomes will be umbilical arterial and venous pH and lactate level, venous base deficit, and Apgar scores at 1 and 5 minutes. Umbilical cord blood gas values, and other relevant anaesthesia data from patients not requiring vasopressor, and for the entire study cohort, will also be collected, so that the study also will also serve as an audit of practice. A maternal arterial blood gas specimen will be obtained immediately after delivery. The number of fetuses with pH < 7.2 will be recorded, as well as those with an umbilical arterial base deficit >10 $mmol \cdot L^{-1}$. At birth, the neonatal weight, gender, gestational age, one and five minute Apgar score, and degree of resuscitation (face mask ventilation, intubation and ventilation, cardiopulmonary resuscitation) will also be recorded. In addition, the number of neonates who develop high-grade intraventricular haemorrhage or hypoxic ischaemic encephalopathy will be recorded.

Statistical analysis:

The primary outcome variable will be the fetal base deficit. Sample size was calculated as follows: A previous study performed at our institution reported an umbilical arterial base deficit of 8.7 $\pm$ 4.0 mEq/L during spinal anaesthesia in patients with severe preeclampsia and a non-reassuring fetal heart trace. In this study, ephedrine was used as the vasopressor.[9] A between group difference of 3 mEq/L was hypothesised as clinically relevant for the current study. Assuming a base deficit of 5.7 $\pm$ 3 mEq/L in the

comparator group (phenylephrine), 31 patients would be required in each group for 90% power to detect this difference. Therefore 32 patients will be included in each group. The null hypothesis is that the vasopressor used will make no difference to neonatal umbilical arterial base deficit in patients with severe preeclampsia. It is estimated from a previous study and from our clinical experience, that 40% of patients will require a vasopressor pre-delivery. Hence 160 patients will be recruited. The 2 sample t-test will be used for the statistical comparison of the two randomised groups with respect to the primary outcome and other continuous variables and the mean difference and 95% confidence intervals will be estimated. For categorical outcomes, Fisher's exact test will be used to compare the proportions.

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PART B: LITERATURE REVIEW

1. Objectives

The aim of the information presented below is to present a narrative review of the currently available literature regarding the use of ephedrine and phenylephrine in the prevention and treatment of spinal hypotension. The information as regards both elective and emergency caesarean deliveries will be presented. Specific focus will be on the fetal effects as the primary outcome of the study will be the effects of the two agents on neonatal base excess. This review will include a discussion on the haemodynamic effects of spinal anaesthesia for caesarean section as well as the pharmacodynamics of ephedrine and phenylephrine. Reference will be made to the definition and the pathogenesis of preeclampsia and studies regarding spinal anaesthesia in severe preeclampsia and the use of vasopressors will be reviewed.

2. Literature Search Strategy

The full text of relevant publications was obtained online, from the University of Cape Town Health Science Library search facility. Literature published between the years 1960 and 2016 was included. In total 47 relevant papers were identified. Literature not published in the English language was excluded.

3. Quality criteria

The keywords used for the search, included each of the following, in various combinations: phenylephrine, ephedrine, spinal anaesthesia, caesarean delivery, hypotension, neonatal blood gas, preeclampsia, acidosis, emergency, urgent. Using reference lists, further appropriate papers were identified.

4. Summary of the literature

4.1. Introduction

Spinal anaesthesia has become the preferred method of anaesthesia for caesarean delivery (CD). In comparison to general anaesthesia, it is perceived as being safer as it avoids potential difficulties with airway manipulation. Spinal anaesthesia has also been shown to be safe and effective in patients with preeclampsia, many of whom have the greatest risk factors for undergoing general anaesthesia.[1] However, spinal anaesthesia is not without its own hazards. The most common side effect is hypotension with its attendant morbidity for both mother and fetus. The best methods of treating and preventing spinal hypotension have been a subject of investigation and debate for decades. Vasoactive drugs are an essential component of this.

The majority of studies have centred around the two most commonly used drugs: ephedrine and phenylephrine. Traditionally, ephedrine was advocated as the treatment of choice based on animal studies in pregnant ewes that demonstrated superior maintenance of uterine blood flow and placental perfusion.[2] However, cumulative evidence over the past two decades has shown that phenylephrine is not only more efficacious in preventing and treating spinal-induced hypotension, it is also associated with a lower incidence of neonatal acidosis.[20,21,23-25,29] The majority of this evidence is from studies performed in healthy patients undergoing elective CD. There is less evidence to support one vasopressor above the other in regards to managing spinal hypotension in cases of actual or possible fetal compromise and/or utero-placental insufficiency. Umbilical cord pH has been shown to have a substantial association with neonatal mortality and morbidity with a four times increase in mortality if the pH is <7.2.[3] Thus, it is of utmost importance to endeavour to avoid a deterioration in neonatal condition though prompt and physiologically appropriate treatment of hypotension with agents that are likely to maintain the optimal balance between fetal oxygen supply and demand. This is of particular significance in neonates with fetal compromise, especially those born to mothers diagnosed with severe preeclampsia who are likely to have pre-existing utero-placental insufficiency.

4.2 Spinal hypotension

Hypotension during spinal anaesthesia for CD is multifactorial. It may be compounded by relative or absolute hypovolaemia, aorto-caval compression, or underlying maternal cardiac disease. However, it is mainly the consequence of sympathectomy-induced vasodilatation predominately affecting the arterial circulation.

The pathophysiology of this sympathectomy has been elucidated. Studies utilising minimally invasive cardiac output monitoring have shown that neuraxial blockade typically results in a decrease in systemic vascular resistance (SVR) with a partial compensatory increase in cardiac output (CO) brought about by increases in heart rate (HR) and stroke volume (SV).[4,5]

Any strategy to counteract spinal hypotension and optimise fetal condition should take into account three factors, namely: reversing the above mentioned pathophysiological changes, optimising utero-placental blood flow, and preventing unfavourable direct fetal effects.

Most patients undergoing elective CD will require a vasopressor to achieve this. The vasopressor should be chosen based on maternal and fetal side effects, maternal haemodynamic effects and efficacy and titratability of the agent.

The two vasopressors predominantly in use in clinical practice are ephedrine and phenylephrine.

4.3 Vasopressors:

4.3.a Ephedrine

Ephedrine is a direct acting β receptor agonist, with indirect α and β effects as a result of the stimulation of noradrenaline release from sympathetic nerve terminals.[6] The end effect of ephedrine administration is an increase in HR, CO and mean arterial pressure (MAP). The perceived advantage of ephedrine for the treatment and prophylaxis of spinal hypotension came about largely as a result of a study in pregnant ewes.[2] In this study, use of pure α agonists was shown to cause uterine artery vasoconstriction and a decrease in placental blood flow. With ephedrine administration, uterine blood flow was unchanged. There was however no significant change in terms of fetal blood gas and acid-base variables.

However, it has been noted that various differences in human and sheep anatomy and physiology make this finding less relevant in clinical practice.[7] The human placenta is a low pressure haemochorial system with a relatively thin barrier to diffusion between the maternal and fetal side. During pregnancy, the uterine arteries are maximally dilated as a result of increased nitric oxide and prostacyclin production as well as a reduced sensitivity to the effects of circulating catecholamines. The spiral arteries supplying the intervillous space are remodelled by invading fetal cytotrophoblasts, becoming significantly enlarged and losing the ability to vasoconstrict. Blood flow is therefore pressure dependent and thus, the concerns regarding α agonist induced vasoconstriction are less relevant than ensuring preservation of systemic pressure.[8]

In contrast, the sheep placenta is a high pressure epitheliochorial system that does not undergo the same remodelling. Denervation of the uterine artery also occurs but is accompanied by an increase in sensitivity of the postsynaptic α adrenergic receptors. Thus in the sheep model catecholamines may cause more uterine than systemic effects.[7]

In addition, most animal studies have been performed under varying circumstances that make their results difficult to compare to humans undergoing neuraxial anaesthesia. For example, the ewes in these studies either received no anaesthesia, general anaesthesia or a combination of the two. Only one study used spinal anaesthesia alone. The doses of vasopressor used were also greater than those used in clinical practice.[9]

Human studies are available comparing the effects of ephedrine vs. phenylephrine and other α agonists on the uteroplacental circulation using the doppler derived pulsatility index as a measure of vascular resistance. Results are conflicting. Alahuhta et al. compared ephedrine and phenylephrine and reported that in patients receiving phenylephrine, mean maternal uterine and placental arcuate artery pulsatility index values were increased compared to the baseline.

This did not occur in patients receiving ephedrine.[10] In contrast, Ngan Kee et al demonstrated in a 2001 study that there was no significant difference in uterine artery pulsatility index between patients who received prophylactic ephedrine or metaraminol infusions (an α agonist with similar effects to phenylephrine).[11]

Ephedrine demonstrates low efficacy for restoration of blood pressure.[12] Ephedrine has a relatively slow onset to peak effect compared to phenylephrine (median 78 seconds [sec] vs. 27 sec using beat-by-beat finger arterial pressure, p=0.006).[13] A 2009 study of haemodynamics using pulse wave analysis demonstrated that it took approximately 40 sec for phenylephrine to restore MAP following spinal anaesthesia, compared to 90 sec for ephedrine.[5]

Ephedrine has also has been found to be less effective for prevention of nausea and vomiting during spinal anaesthesia for CD.[21-24,26] It has the sometimes unwanted side effect of tachycardia. In addition, continued use results in tachyphylaxis to the indirect actions.[14]

4.3.b Phenylephrine

Phenylephrine is a short acting, rapid onset, potent, direct acting α agonist synthetically derived from adrenaline.[15]

As already stated, the typical response to spinal anaesthesia for CD, is a reduction in SVR with a partial compensatory increase in HR and CO.[5]

In most cases, the spinal-induced decrease in SVR may be effectively prevented or treated by the use of either low-dose boluses or a low-dose infusion of phenylephrine thereby restoring baseline blood pressure, HR and CO. Dyer et al suggest that HR should be taken as a surrogate of CO and to titrate phenylephrine to restore CO to baseline in healthy elective patients.[5] However, doses that cause an increase in MAP above baseline with sinus bradycardia may be associated with a decrease in CO and should be avoided. It is postulated that significant reductions in CO may have the potential to harm a compromised fetus with little reserve.[16,17]

Studies of umbilical arterial gases from neonates whose mothers received high dose phenylephrine infusions to maintain MAP have shown that pH and base excess (BE) values are well preserved, even when given in high doses.[17] This observation suggests that despite the potential for uterine artery vasoconstriction observed in animal studies, phenylephrine preserves blood flow by an increase in uterine perfusion pressure.

Phenylephrine has however been shown to decrease umbilical venous oxygen partial pressure ($UVPO_2$) which could suggest a reduction in flow due to vasoconstriction.[22,24] Again, this has not been correlated with a worsening of fetal acid base status or Apgar scores possibly because of the existence of significant placental reserve for oxygen delivery.[7] Animal studies have shown

that uterine artery blood flow is higher than that required by fetal demand and is thus able to provide a margin of safety.[18]

In summary, phenylephrine has been shown to be effective in restoring vascular tone to normal during spinal anaesthesia for CD without an adverse effect on fetal oxygen supply demand balance.[19]

4.4 Phenylephrine vs. Ephedrine for the treatment and prophylaxis of spinal-induced hypotension:

4.4.a Elective cases

A systematic review of ephedrine vs. phenylephrine for the management of hypotension during spinal anaesthesia for CD was published by Lee et al in 2002.[20] This identified 7 randomised controlled trials over the period 1966 to 2001. Neonates whose mothers were given phenylephrine had higher umbilical pH values that those whose mothers were treated with ephedrine. However, there was no difference in the incidence of a pH <7,2 (seen as true fetal acidosis) and no difference in Apgar scores less than 7 at 1 and 5 minute intervals. The difference in the pH was not shown to be clinically significant. They concluded by challenging the traditional view that preferred the use of ephedrine over phenylephrine. Of note, all the patients in the included studies were reported to be healthy and non-labouring.

Multiple trials in healthy, ASA 1-2 women undergoing elective CD followed on from this in an attempt to better define the effect of the two vasopressors on fetal outcome (with UApH and BE as a proxy).

Cooper et al in a RDBT in 2002 demonstrated a significantly lower UApH and BE with ephedrine as well as an increased risk of an UApH <7,2.[21] Patients were recruited to receive either a phenylephrine infusion, an ephedrine infusion or a combination of the two to maintain systolic blood pressure (SBP) at baseline. Only 1 of the 48 neonates in the phenylephrine group, and 1 of the 47 in the combination group were acidotic, compared with 10 of 48 in the ephedrine group. Of note in this study, the patients were likely to have received relatively large doses of ephedrine as infusions were used (mean dose 1,5 mg/min) and the spinal to delivery interval ranged between 24-30 minutes. The cord blood gases in the ephedrine arm were also noted to have a greater umbilical arterio-venous partial pressure of carbon dioxide difference [(A-V) PCO_2] which correlated with increasing ephedrine dose. The authors postulated that the mechanism for the decrease in pH may be an increase in fetal metabolism as a result of a direct effect of ephedrine. There was however no difference in Apgar scores, neonatal outcome or admission to the neonatal unit. However, the authors did raise concern that in compromised fetus's the increase in metabolism may be detrimental to those at the limit of their reserve.

The mechanism of acidosis was further elucidated in a 2009 study.[22] A comparison was made of various biochemical indices between neonates whose mothers were exposed to either phenylephrine or ephedrine infusions. These included UA pH, BE, PCO_2, UV PO_2,UA/UV plasma lactate difference, glucose, adrenaline and noradrenaline concentrations.

In the ephedrine group, UA and UV pH and BE were lower; and in addition, concentrations of lactate, glucose, adrenaline and noradrenaline were greater. Umbilical arterial PCO_2 and UV PO_2 were also greater in the ephedrine group. Placental transfer was significantly greater for ephedrine and it appeared to undergo less metabolism or redistribution in the fetus than phenylephrine (median umbilical venous/maternal arterial concentration ratio 1.13 versus 0.17).

This supported the hypothesis that the effects of ephedrine on acid base were due to transfer across the placenta and direct stimulation of fetal β receptors resulting in an increase in fetal metabolism.

Further randomised controlled trials in elective CD continued to show significantly decreased UApH and UABE values in neonates exposed to ephedrine whether as a continuous infusion or as boluses.[5,22-26]

The total dose of ephedrine given correlates with worsening fetal acid-base profile. [24,25] However even at lower doses, there is still a trend towards a lower fetal pH.[8] It may be possible that some fetuses are more at risk of developing a clinically significant acidosis in response to ephedrine exposure based on their genetic profile. In a randomised study of Chinese women receiving either ephedrine or phenylephrine infusions, neonatal birth weight and genotype but not ephedrine dose were found to predict neonatal acidosis. This was dependent on the β2 adrenoreceptor haplotype. Neonates that were homozygous for Arg16 were protected from developing an acidosis when their mothers were treated with ephedrine.[27] Therefore even small doses of ephedrine may result in significant acidosis in susceptible neonates despite the fact that the average UApH and BE in a given cohort may be unaffected.[8]

A recent systematic review and cumulative meta-analysis in 2012 clearly showed a decreased risk for fetal acidosis with the use of phenylephrine. In fact, the relative risk of true fetal acidosis (pH <7,2) was 5,29 for ephedrine vs. phenylephrine (p=0,006).[29]

4.4.b Emergency cases

It is important to consider the adverse effects that vasopressor treatment could have on a potentially compromised fetus. A fetus with an already impaired utero-placental circulation may not be able to compensate for any further reduction in flow due to vasoconstriction or decreased CO. Equally, it may not be able to cope with the increase in oxygen demand as a result of ephedrine stimulated increases in metabolism.

In this situation, animal studies again have suggested a preference for ephedrine. Erkinaro et al studied the effects of phenylephrine and ephedrine for the treatment of hypotension in a sheep model of increased vascular resistance.[30] These sheep were rendered hypoxic and hypotensive. Both ephedrine and phenylephrine were able to restore haemodynamics. However, ephedrine did so without any deterioration in fetal lactate concentration while the phenylephrine group demonstrated a continued deterioration in lactate values.

This has not been replicated in the few human studies in the literature.

Ngan Kee et al, in 2008, conducted a randomised comparison of bolus phenylephrine and ephedrine for treating hypotension under spinal anaesthesia for non-elective CD.[31] They found that UA and UV pH and BE were similar. UA and UV lactate were higher in the ephedrine group. UV and UA p02 was lower in the phenylephrine group but oxygen content was similar. There was no difference in Apgar scores or clinical outcome. They concluded that both vasopressors were suitable for use in non-elective CD.

Importantly, the patients enrolled were ASA status 1/2 with term pregnancies. No patients enrolled were diagnosed with preeclampsia. The median dose of ephedrine received was 10 mg (IQR 10-30 mg) which was small in comparison to doses used in previous studies in elective cases.

Of 204 patients; 148 patients received a vasopressor and, of those 30 were deemed to have fetal compromise. Sub-analysis of this group showed that $UAPO_2$ was lower in the phenylephrine group but all other gas parameters and lactate values were similar. The authors postulated that this may reflect vasoconstriction, reduced uteroplacental blood flow and increased fetal oxygen extraction.

Cooper et al published a retrospective study of the association between choice of vasopressor and fetal pH during high risk CD (defined as CD for “non-reassuring fetal heart rate tracing (NRFHRT), dystocia, pregnancy-induced hypertension, growth restriction, antepartum haemorrhage, prolonged rupture of membranes, or cord prolapse”).[32]

UApH was similar whether ephedrine or phenylephrine was used. Using multiple regression analysis, they identified that the only variable associated with a low pH was a NRFHRT. They concluded that the likely reason for the similar pH between groups was that a lower total dose of ephedrine (mean 12 mg [IQR 6-8 mg]) had been given in comparison to previous studies in elective cases.

A more recent study compared ephedrine 8 mg and phenylephrine 100 µg in a group of healthy patients undergoing emergency CD for fetal compromise. They found no between-group

differences in UA and UV pH, PO_2, PCO_2, BE, or the incidence of fetal acidosis. Apgar scores and early fetal outcome were also comparable.[33]

There is a lack of studies addressing the question of whether phenylephrine or ephedrine is associated with an improved acid/base profile when used for spinal-induced hypotension in patients with severe preeclampsia and fetal distress.

4.5 Preeclampsia

Preeclampsia is a unique maternal multi-systemic disease that manifests after 20 weeks of gestation. The diagnostic criteria are as follows:

1.) A blood pressure greater than or equal to 140 mmHg systolic or greater than or equal to 90 mmHg diastolic on two occasions at least 4 hours apart in a woman with a previously normal blood pressure.

2.) Proteinuria greater than or equal to 300 mg per 24 hours or a protein/creatinine ratio greater than or equal to 0,3 (or dipstick of 1+ or greater if other quantitative methods are not available).[34]

In the absence of proteinuria, preeclampsia is diagnosed when there is new onset hypertension with any of the following: thrombocytopaenia, renal insufficiency, impaired liver function, pulmonary oedema, cerebral or visual symptoms. The presence of these features is a marker of severe disease.

The disease may otherwise be considered severe when there is a SBP of 160 mmHg or higher, or diastolic blood pressure (DBP) of 110 mmHg or higher on two occasions at least 4 hours apart while the patient is on bed rest (unless antihypertensive therapy is initiated before this time).

The hypertension of preeclampsia is characterised by peripheral vasoconstriction and reduced arterial compliance.[35] Patients also develop cardiac dysfunction, most commonly diastolic dysfunction. [36,37] Inotropy is often preserved or even increased. However, cases of severe left ventricular dysfunction and global biventricular systolic dysfunction also occur (Melchiorre, 2012).[37]

There is a distinction between early onset (less than 34 weeks gestation) and late onset disease (greater than or equal to 34 weeks gestation). Women with early onset disease are more likely to develop severe pre-eclampsia, HELLP syndrome and eclampsia than those with late onset disease (adjusted odds ratio [aOR] 5,8). In addition, fetal death is more likely with an aOR of 1,3.[38]

Early onset preeclampsia is associated with a higher SVR, lower CO and worse myocardial impairment - systolic and diastolic.[39,40] Neonates born to mothers with preeclampsia may suffer intrauterine growth restriction (IUGR), oligohydramnios or problems related to prematurity as a result of the necessity for preterm delivery. Interestingly, they are less likely to demise in the neonatal period compared to babies born at the same gestational age to woman without preeclampsia.[38]

The pathogenesis of preeclampsia is complex and still a subject of ongoing research. There is evidence that the end result of the pathophysiological process is damage to the vascular endothelium including the endothelium of the glomerular capillaries and the choroid plexus. It is thus a multi-system disease affecting the renal, hepatic, neurologic, cardiac, pulmonary and uteroplacental systems.

The placenta maintains a key role in the pathogenesis with abnormalities of placental development preceding any detectable maternal features.[35]

Normal placentation involves invasion of the uterine wall and decidual vessels by the embryonal cytotrophoblasts. These cells undergo cellular mimicry, adopting an endothelial phenotype and inducing maternal decidual vessel remodelling to form high capacitance, low resistance vessels. This process is incomplete in preeclampsia. The cytotrophoblasts do not invade beyond the superficial layers of the decidua and remodelling does not take place; resulting in constricted, high resistance vessels.

Abnormal uterine artery Doppler waveforms suggestive of decreased placental perfusion have been shown to herald the development of preeclampsia and placental hypoxia is implicated in the development of the disease in the mother.[41]

There are multiple homeostatic mechanisms at work to maintain a healthy endothelium. Disruption to the normal balance between anti and pro-angiogenic factors in pregnancy may be the final common pathway to the development of disease. Recently identified circulating anti-angiogenic proteins (specifically soluble fms-like tyrosine kinase [sFlt-1] and soluble endoglin [sEng]) released from the abnormal placenta have been implicated in this disruption. There is an imbalance between these and the effects of pro-angiogenic factors (VEGF, PlGF, and TGF-b). It is this imbalance which results in the features of the maternal disease and may result in an increased risk of cardiovascular disease in later life.[35]

4.6 Severe Preeclampsia and Spinal Anaesthesia:

Patients with severe preeclampsia have less frequent and less severe hypotension in response to spinal anaesthesia.[38,42] As a result, they often require reduced doses of

vasopressors. However, at the same time they are vulnerable to a reduction in uteroplacental perfusion.

There have been no prospective studies published to date specifically examining the effects of phenylephrine vs. ephedrine on neonatal outcome when used to counteract spinal hypotension in mothers with severe preeclampsia and fetal distress. The majority of studies regarding spinal anaesthesia for severe preeclampsia in the literature have compared either spinal with epidural anaesthesia or spinal with general anaesthesia.[43-45]. All these studies have used ephedrine to counteract predetermined levels of hypotension. Visalyaputra et al. found that patients randomised to receive spinal anaesthesia had double the incidence of significant hypotension than their epidural counterparts. However, the duration of hypotension was short. The spinal anaesthesia cohort received significantly more ephedrine (0-18 mg [0] vs 0-36 mg [6]) but there was no difference in neonatal acid base indices or in Apgar scores.[43]

A study published in 2003 compared general anaesthesia vs spinal for CD in preeclamptic patients with a NRFHRT.[45] Neonates born to mothers randomised to spinal anaesthesia had significantly higher base deficits and lower pH values despite similar haemodynamics. All patients received ephedrine for hypotension but significantly more was required in the spinal group (13,7 mg vs 2,7 mg P=0.002). However, there was no correlation between ephedrine use and neonatal base deficit in either group and, there was no correlation between ephedrine use and neonatal base deficit in the spinal group overall and in particular in the case of neonates with a base deficit more than 10 mmol/l. Interestingly, a subgroup analysis showed a significant difference in base deficit only when maternal DBP was greater than 110 mmHg. However, the significance is unknown as the study was not powered to assess this group of patients.

In severe pre-eclampsia haemodynamic goals during anaesthesia are to optimise maternal BP and CO as well as uteroplacental perfusion. Dyer et al. investigated the haemodynamic changes associated with spinal anaesthesia and the administration of phenylephrine for CD in severe pre-eclampsia with the use of beat to beat cardiac output monitoring (LiDCOPlus). [46] When MAP decreased to less than 20% of baseline, SVR was also shown to be significantly below baseline but CO and HR did not differ. The administration of phenylephrine resulted in a significant increase in SVR and MAP. Heart rate decreased significantly but SV and CO did not change. The main effect of spinal anaesthesia was concluded to be a modest reduction in afterload. Phenylephrine administration was associated with a trend towards a reduction in CO but the mean change was not significant. No observations were made regarding uteroplacental perfusion but the median (range) UApH was 7,28 (7,19-7,31) and the mean (SD) BD was -3,1 (1,9) mmol/l.

Ituk, Cooter and Habib undertook a retrospective comparison of bolus administered ephedrine and phenylephrine for the treatment of spinal-induced hypotension in preeclamptic patients undergoing CD in their institution between January 2005 and July 2014.[47] The primary outcome was umbilical arterial pH. One hundred and forty six patients were included in the analysis. The results showed no difference in pH whether ephedrine or phenylephrine was used with a median pH of 7,3 (IQR 7.20-7.30) in both groups (P=0.41). There was also no significant difference in base excess, 1 min and 5 min Apgar scores or in the number of neonates with an UApH <7.2. They noted in their discussion that the majority of cases were classified as category I/II CDs (in accordance with the Royal College of Obstetricians and Gynaecologists) and thus the urgent nature of the case likely resulted in a shorter interval between induction of spinal anaesthesia and delivery. In comparison to most of the previously performed elective studies, this would have resulted in less vasopressor being required pre-delivery and specifically less fetal exposure to ephedrine.

The comparison was however limited by its retrospective nature. There were significant differences between the two groups in terms of patient characteristics, the indications for CD and the doses of vasopressor used.

More patients in the phenylephrine group were classified with severe preeclampsia (98.9%) compared to the ephedrine group (82.5%) (p=0.0004). The neonates in the ephedrine group had a lower gestational age (32 weeks vs. 36 weeks; p=0.002) and had a lower birthweight (1.8 kg vs. 2.6 kg; p=0.03).

77% of deliveries in the ephedrine group and 81% in the phenylephrine group were classified as category I or II (P=0.59). However, in the breakdown of indications for delivery, 17.5% of the ephedrine group had a NRFHRT compared to 3.4% of the phenylephrine group. Severe preeclampsia alone was an indication in 49.1% of the ephedrine group and 85.4% in the phenylephrine (p<0.0004).

Lastly, the median dose of vasopressor used was lower in the ephedrine than the phenylephrine groups.

Multivariate regression analysis showed a NRFHT to be the only variable associated with a significantly lower UApH.

4.7 Conclusion:

Hypotension in response to spinal anaesthesia may be a result of a number of differing factors: sympathetic blockade, aortocaval compression, underlying intravascular depletion and possible left ventricle dysfunction. With this in mind, it is important to select a treatment (vasopressor) that is physiologically appropriate to the derangements within the index patient.

There are many influences on the neonatal outcome after CD in patients with preeclampsia including the severity of disease, the degree of uteroplacental insufficiency, the treatment received and the anaesthesia and surgical management. In the context of these many factors, it is not known whether the treatment of spinal induced hypotension with phenylephrine or ephedrine has any impact on the neonatal outcome. Studies in elective healthy patients have clearly shown that ephedrine results in more fetal acidosis, whereas studies of non-elective cases have found no difference. This would be the first randomised comparison of the effect on acid base values and early neonatal outcome of the use of phenylephrine vs. ephedrine for spinal hypotension in patients with severe preeclampsia and a NRFHRT.

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PART C: MANUSCRIPT

TITLE PAGE

A randomised comparison of bolus phenylephrine and ephedrine for the management of spinal hypotension in patients with severe preeclampsia and fetal compromise

Dr. Samantha C. Adams, MBChB
Prof Robert A. Dyer, MBChB, FCA (SA), PhD

Groote Schuur Hospital, University of Cape Town, Anzio Road, Observatory, Cape Town, South Africa

Corresponding Author: Dr. Samantha Adams, D23 Anaesthesia Department, Groote Schuur Hospital, Anzio Road, Observatory, 7935, Republic of South Africa. Adams.scl@gmail.com +27 21 404 5001

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Declaration of interests

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Abstract

Background: Studies in healthy patients undergoing elective caesarean delivery show that ephedrine used for spinal hypotension is associated with increased fetal acidosis compared with phenylephrine. This has not been investigated prospectively in severe preeclampsia.

Methods: Patients with severe preeclampsia requiring caesarean delivery for a non-reassuring fetal heart tracing were randomised to receive bolus ephedrine (7.5-15 mg) or phenylephrine (50-100 μg) for spinal hypotension. The primary outcome was umbilical arterial base deficit. Secondary outcomes were umbilical arterial (UA) and venous (UV) pH and lactate level, venous base deficit, and Apgar scores.

Results: A total of 133 women were included; 64 required vasopressor treatment and were randomised to 2 groups of 32 with similar patient characteristics. Pre-delivery blood pressure changes were similar in the 2 groups. There was no difference in mean [SD] UA base deficit (-4.9 [3.7] vs -6.0 [4.6] $mmol \cdot L^{-1}$ for ephedrine and phenylephrine respectively; $P = 0.29$). Mean [SD] pH (UA and UV) and lactate levels were also similar between groups (7.25 [0.08] vs 7.22 [0.10], 7.28 [0.07] vs 7.27 [0.10], and 3.41 [2.18] vs 3.28 [2.44] $mmol \cdot L^{-1}$ respectively). In addition, UV PO_2 was higher in the ephedrine group (2.8 [0.7] vs 2.4 [0.62]) kPa, $P = 0.02$). There was no difference in 1- or 5-minute Apgar scores, numbers of neonates with 1-minute Apgar scores < 7 (10/32 [31%] vs 12/32 [38%]), or with a pH < 7.2 (6/31 [19%] vs 8/29 [28%]).

Conclusions: In patients with severe preeclampsia and fetal compromise, fetal acid-base status is independent of the use of bolus ephedrine vs phenylephrine to treat spinal hypotension.

Keywords: ephedrine, fetal compromise, phenylephrine, preeclampsia, spinal hypotension, vasopressor

Trial Registry Number: South African National Clinical Trial Register (DOH -27-111-3888).

Main Text

Introduction

Spinal hypotension during caesarean delivery remains a significant clinical challenge; maternal nausea and vomiting and fetal compromise may result. Ephedrine and phenylephrine are commonly used to prevent and treat spinal hypotension. In healthy patients with no fetal compromise, ephedrine is associated with more fetal acidosis than phenylephrine.[1] The clinical significance of this difference is likely minimal unless large doses are administered.[2] One study suggests that acidosis may arise after low doses of ephedrine in genetically susceptible individuals.[3] There is limited data regarding vasopressor use in mothers with a compromised fetus or placental function.[4-7] In these women it is possible that the unfavourable oxygen supply-demand ratio caused by ephedrine-induced increased fetal metabolic rate may be deleterious.

In women with preeclampsia, spinal anaesthesia is associated with less hypotension than in healthy patients.[8] Typically, it causes modest afterload reduction, which may be beneficial.[9] However, clinically significant hypotension may occur in some patients. A retrospective comparison of the use of phenylephrine and ephedrine during spinal anaesthesia for caesarean delivery in women with preeclampsia, included women with both maternal and fetal indications for delivery.[6] There were no between-group differences in umbilical arterial pH.[6] The aim of our randomised trial was to compare the use of bolus ephedrine and phenylephrine for the treatment of spinal hypotension in women with severe preeclampsia with a non-reassuring fetal heart tracing undergoing caesarean delivery. The primary outcome variable was the umbilical arterial (UA) base deficit. Secondary outcomes were umbilical arterial and venous (UV) pH and lactate level, venous base deficit, and Apgar scores at 1 and 5 minutes. Overall results for the entire cohort of recruited patients, including those not requiring vasopressor pre-delivery, are also presented.

Methods

The study commenced after the approval of the Health Science Faculty Human Research Ethics Committee of the University of Cape Town. It was registered with the South African National Clinical Trial Register before the start of recruitment (DOH -27-111-3888), and performed at the New Groote Schuur Hospital Maternity Centre. Informed written consent was obtained immediately after the patient was scheduled for caesarean delivery. Fetal cardiotocography was interpreted by the obstetricians,

according to the guidelines of the Royal College of Obstetricians and Gynaecologists.[10] Patients with severe preeclampsia requiring caesarean delivery for a non-reassuring fetal heart tracing were recruited.

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.[11] At the time of initiation of the present study, preeclampsia was diagnosed if the diastolic blood pressure after 20 weeks' gestational age was greater than or equal to 90 mmHg on two separate occasions at least 4 hours apart, and there was proteinuria of 2+ on urine dipstix 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 exceeded 110 mmHg, obtained on at least two separate occasions, or if the patient had symptoms of imminent eclampsia (severe headache, visual disturbance, epigastric pain, hyperreflexia), or proteinuria on urine dipstix of 3+ or more.

Maternal exclusion criteria were patient refusal, any contraindication to spinal anaesthesia, body mass index greater than 40 $kg \cdot m^{-2}$, clinical signs of hypovolaemia, abruptio placentae, placenta praevia, coagulation abnormality, thrombocytopaenia (platelet count < $75x10^{9} \cdot L^{-1}$), pulmonary oedema, local or generalised sepsis, spinal deformity, umbilical cord prolapse, prior non-obstetric abdominal surgery, more than 2 previous caesarean deliveries, or patients who were HIV positive and had AIDS-defining disease at the time of recruitment. Fetal exclusion criteria were persistent fetal bradycardia or any other fetal condition contraindicating spinal anaesthesia, gestational age < 28 weeks, estimated fetal weight < 900 g, and twin pregnancy. Patients were excluded from data analysis if initiation of spinal anaesthetic took longer than 20 minutes; in this case, the patient received general anaesthesia and failure of the technique was recorded.

Antepartum management followed the established protocols of our institution: if the patient was in established labour, an intravenous line was inserted, and a balanced crystalloid solution was administered at less than 100 mL per hour. Patients not in labour were allowed free oral fluids. Magnesium sulphate ($MgSO_4$) seizure prophylaxis was administered to patients with severe preeclampsia (intravenous loading dose of 4 g followed by 1 $g \cdot h^{-1}$). Dihydralazine was administered intravenously for additional blood pressure control according to a standardised protocol. Prior use of other agents (alpha methyldopa, morphine and dexamethasone) was recorded.

When a decision was made to proceed to caesarean delivery, the patient was placed in the left lateral position before transfer to the operating theatre; 40% oxygen was delivered by face-mask.

All patients received 30-mL oral sodium citrate in theatre, as well as 1-g intravenous cefazolin prior to induction of spinal anaesthesia. Monitoring consisted of electrocardiograph, non-invasive blood pressure and pulse oximetry. Baseline mean arterial pressure (MAP) was recorded as the mean of two non-invasive blood pressure readings not differing by more than 10%, measured in the 5 minutes prior to induction of spinal anaesthesia in the left lateral position. After calculation of the mean baseline blood pressure, the target value for administration of vasopressor was calculated. Thereafter an intravenous fluid preload of 300-mL hydroxyethyl starch (Voluven®) was rapidly administered. Haemodynamic data were recorded every minute after initiation of spinal anaesthesia until delivery; thereafter the time intervals for haemodynamic monitoring until the end of the procedure was at the discretion of the attending anaesthesiologist.

The management of spinal anaesthesia was as follows: 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 in the absence of uterine contractions. After 20 seconds in the sitting position, patients were positioned supine with left lateral tilt, to minimise aortocaval compression. Block height was assessed using cold sensitivity to ethyl chloride spray, and surgery commenced when a block level of T4 was achieved. All mothers received 40% oxygen by face-mask during their surgery.

The management of hypotension was as follows: Patients were randomised to receive either ephedrine or phenylephrine at the time that a vasopressor was required. Blocked randomisation was used (randomised block sizes of 4, 6 or 8 using nquery Advisor Version 6, Statistical Solutions, Cork, Ireland). Sealed envelopes were prepared by the statistician and were opened if the patient became hypotensive. 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. Ephedrine 7.5 mg or phenylephrine 50 µg in a volume of 1,5 mls each, was administered in response to a 20% decrease from baseline mean arterial pressure (MAP) if the MAP was also less than 110 mmHg (target value). If MAP was not restored to the target value within 60 – 90 seconds, a second bolus of 7.5 -15 mg ephedrine or 50-100 µg phenylephrine, as per the randomisation schema, was administered. 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. If the MAP at any point decreased to more than 30% below baseline, 15 mg ephedrine or 100 µg phenylephrine was administered. If heart rate 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..

Twenty seconds after delivery, oxytocin 3.0 IU in 3-mL saline, was administered over a period of 60 seconds. Umbilical arterial and venous blood samples were collected from a segment of double-clamped umbilical cord shortly after delivery, and arterial and venous blood gas parameters were determined. Blood gas analysis was performed using the ABL800 Flex Analyser (Radiometer Copenhagen, Denmark).

After delivery, phenylephrine 50 -100 µg or ephedrine 7.5 – 15 mg was administered in boluses to maintain MAP above 90 mmHg.

Clinically relevant times were recorded: a) decision for caesarean delivery, b) arrival in theatre, c) induction of anaesthesia (intrathecal injection), d) uterine incision time, e) delivery.

All maternal medication 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), and presence or absence of labour were also recorded. Maternal side-effects, in particular nausea and vomiting, were noted. Neonatal outcome was assessed by a paediatrician dedicated to the study, and blinded to the vasopressor used.

The primary outcome was umbilical arterial base deficit. Secondary outcomes were umbilical arterial and venous pH and lactate level, venous base deficit, and Apgar scores at 1 and 5 minutes. Umbilical cord blood gas values, and other relevant anaesthesia data from patients not requiring vasopressor, and for the entire study cohort, were also collected. A maternal arterial blood gas specimen was obtained immediately after delivery. The number of fetuses with pH < 7.2 was noted, as well as those with UA base deficit >10 $mmol \cdot L^{-1}$. In addition, the number of neonates requiring tracheal intubation and/or who developed high-grade intraventricular haemorrhage or hypoxic ischaemic encephalopathy was noted.

Statistical analysis

The primary outcome variable was the umbilical arterial base deficit. The a priori sample size was calculated as follows: A previous study performed at our institution reported an umbilical arterial base deficit of 8.7 ± 4.0 mmol·L^{-1} during spinal anaesthesia in patients with severe preeclampsia and a non-reassuring fetal heart tracing. In this study, ephedrine was used as the vasopressor.[12] A between-group difference of 3 mmol.l^{-1} was hypothesised as clinically relevant for the current study. Assuming a base deficit of 5.7 ± 3 mmol·L^{-1} in the comparator group (phenylephrine), 31 patients would be required in each group for 90% power to detect this difference. Therefore, the planned recruitment was 32 patients who received vasopressor in each group. The null hypothesis was that there would be no difference in umbilical arterial base deficit in patients with severe preeclampsia who received ephedrine vs phenylephrine. The 2 sample t-test was used for the statistical comparison of the two randomised groups with respect to the primary outcome and other continuous variables and the mean difference and 95% confidence intervals were estimated. For categorical outcomes, Fisher's exact test was used to compare the proportions.

Results

Details of patient recruitment are shown in the CONSORT diagram (Figure 1). A total of 133 patients were recruited to this randomised trial, and 64 women were randomised to receive either ephedrine or phenylephrine for pre-delivery spinal hypotension. The initial sample size calculation assumed that 40% of patients would require vasopressor pre-delivery. This would have required 160 patients for adequate power. However, 64 patients required the intervention after 133 patients had been recruited, so that the study was concluded at this point. In the ephedrine group, an umbilical venous sample could not be obtained in one patient and an umbilical arterial specimen in a second patient. Umbilical arterial sampling failed in three patients in the phenylephrine group and in one patient, the maternal blood gas sample was venous. Thus, for the primary outcome variable, data from 31 patients in the ephedrine group and 29 in the phenylephrine group were compared. No patient was excluded because the allowed time for spinal anaesthesia was exceeded, and none required general anaesthesia.

Data were also recorded in 69 patients who did not require vasopressor therapy. Four of these were excluded from statistical analysis; 2 were inappropriately recruited (the indication for caesarean delivery was not per protocol) and in a further two there was non-adherence to protocol. In the group not requiring vasopressor therapy, umbilical

arterial specimens were not obtainable in 4 patients. One maternal arterial blood gas sample was not taken, and in one case the mother was breathing room air during sampling.

Demographic data and further relevant anaesthesia data, including mean pre-delivery vasopressor doses, are presented in Table 1. There were no differences between groups with respect to use of non-study medications, numbers of patients in active labour, severity of disease, gestational age, measures of fetal antenatal condition, or relevant time intervals. All patients received 300-mL colloid pre-delivery, and there was no clinically significant haemorrhage. Two patients in the ephedrine group also received the alternative vasopressor phenylephrine, 100 and 400 µg respectively, due to a poor initial pressor response, as per protocol. Block height ranged from T1 to T6, and no patient required supplemental analgesia pre-delivery. Figure 2 depicts pre-delivery blood pressure control in patients in the ephedrine and phenylephrine groups. There were no significant differences.

Table 2 shows details of the umbilical cord and maternal blood gas values, Apgar scores and other neonatal outcomes. There was no significant between-group difference in mean [SD] umbilical arterial base deficit in the ephedrine vs phenylephrine groups (-4.8 [3.7] vs -6.0 [4.6] $mmol \cdot L^{-1}$ respectively). The 95% confidence interval of the difference was -1.0 to 3,3 $mEq \cdot L^{-1}$; $P = 0.29$. There were no differences in mean pH or bicarbonate, PCO_2, lactate levels, or Apgar scores at 1 or 5 minutes. Eight patients in the phenylephrine (28%) vs 6 in the ephedrine group (19%) had an umbilical arterial pH < 7.2, and 4 patients in each group (14% in the phenylephrine vs 13% in the ephedrine group) had a base deficit > 10 $mmol.l^{-1}$ (NS). Mean umbilical venous PO_2 was higher in the ephedrine group (2.8 [0.7] vs 2.4 [0.6] $mmol \cdot L^{-1}$; $P = 0.02$) (Figure 3).

Discussion

This randomised trial examined the effects on fetal acid-base status of bolus ephedrine versus phenylephrine administered in response to spinal hypotension in patients with severe preeclampsia and a non-reassuring fetal heart tracing. There were no differences in umbilical arterial base deficit, or any of the other indices of fetal acidosis. The only difference was a higher umbilical venous PO_2 in the group randomised to ephedrine. Importantly, there were no differences in Apgar scores or other clinical outcomes. This is in agreement with other studies in non-elective caesarean delivery. This study is however unique in that it was specifically designed to assess neonates with potential fetal compromise born to mothers with established severe preeclampsia. This group is at particularly high risk of uteroplacental insufficiency, and therefore concern exists

regarding the possible effects of vasopressors on the uteroplacental circulation. The results of this study employing vasopressors by bolus administration are consistent with the results of a parallel study performed at Northwestern University (Chicago, IL, USA), in which women with preeclampsia undergoing caesarean delivery under spinal anaesthesia were randomised to receive a phenylephrine or ephedrine infusion to prevent the development of hypotension.[13] The investigators for both studies collaborated on the design, analysis and reporting of the studies.

The two vasopressors predominantly in use in clinical practice are the mixed alpha- and beta-adrenergic agonist ephedrine and the direct acting alpha-adrenergic agonist phenylephrine. A significant body of work in healthy, non-labouring women undergoing elective caesarean delivery has found that neonates whose mothers were given phenylephrine for the treatment of spinal hypotension, had higher umbilical arterial pH values that those whose mothers were treated with ephedrine. A recent systematic review and cumulative meta-analysis clearly demonstrated a decreased risk for fetal acidosis with phenylephrine administered to healthy mothers undergoing elective caesarean delivery. The relative risk of fetal acidosis (pH <7.2) was 5.29 for ephedrine vs phenylephrine (P = 0.006).[1]

The mechanism of acidosis was elucidated by Ngan Kee and colleagues.[2] In a randomised comparison, patients receiving ephedrine by continuous infusion had not only lower umbilical arterial and venous pH and a higher base excess than those receiving phenylephrine infusions, but also higher umbilical arterial and venous plasma concentrations of lactate, glucose, adrenaline and noradrenaline. Placental transfer was significantly greater for ephedrine than phenylephrine, supporting the hypothesis that the effects of ephedrine on acid-base status are due to direct stimulation of fetal β-adrenergic receptors, resulting in an increase in metabolic rate.
The total dose of ephedrine appears to correlate with worsening fetal acid-base status.[6, 14] However, even at lower doses, there is still a trend towards a lower fetal pH.[15] It is possible that some fetuses are at higher risk of clinically significant acidosis in response to small doses of ephedrine based on their genetic profile, in particular the β_2-adrenoreceptor haplotype.[3]

It is important to consider the possible adverse effects that vasopressor treatment could have on a fetus with actual or potential compromise. A fetus with a compromised uteroplacental circulation may not be able to compensate for any further reduction in flow due to vasoconstriction or decreased maternal cardiac output induced by vasopressor

therapy. Equally, the fetus may not be able to cope with the increase in oxygen demand as a result of ephedrine-induced increases in metabolism.

There are a limited number of randomised trials examining the effects of bolus phenylephrine vs ephedrine in non-elective caesarean delivery. Ngan Kee and colleagues found similar UA and UV pH and base excess between groups.[4] UA and UV lactate levels were higher in the ephedrine group. UV and UA PO_2 were lower in the phenylephrine group, but O_2 content was similar. There were no differences in Apgar scores and clinical outcome. The authors concluded that either vasopressor was acceptable in the setting of non-elective caesarean delivery. Importantly, the enrolled patients were ASA physical status 1 or 2 with term pregnancies, and none had preeclampsia. The total vasopressor dose was low in comparison to previous studies in healthy women undergoing elective procedures. Of 148 patients receiving vasopressor therapy, 30 were deemed to have fetal compromise. Sub-analysis of this group showed that UA PO_2 was lower in the phenylephrine group, but all other blood gas parameters were similar. It was postulated that these differences in PO_2 may reflect vasoconstriction, reduced uteroplacental flow and increased efficiency of oxygen extraction, which may act as a safety mechanism preventing an adverse impact of phenylephrine on fetal acidosis or Apgar scores. The finding of a lower UV PO_2 in the phenylephrine group has also been shown in the elective setting.[2 16] Our study also found a statistically, but not clinically significantly higher UV PO_2 in the ephedrine group.

A more recent study compared ephedrine 8 mg and phenylephrine 100 µg in a group of healthy patients undergoing emergency caesarean delivery for fetal compromise.[7] They found no between-group differences in UA and UV pH, PO_2, PCO_2, BE, or the incidence of fetal acidosis. Apgar scores and early fetal outcome were also comparable.

Cooper[5] published a retrospective study of the association between choice of vasopressor and fetal pH during high-risk caesarean delivery for various indications. UV PO_2 was again higher in the ephedrine group. UA pH was similar whether ephedrine or phenylephrine was used. The only variable associated with a low fetal pH was a non-reassuring fetal heart rate tracing. They concluded, in agreement with previous studies, that the likely reason for the similar pH between groups was that a lower total dose of ephedrine (mean 12 mg [IQR 6-18 mg]) had been given in comparison with studies in elective cases.

There is only one retrospective comparison of bolus administered ephedrine and phenylephrine for the treatment of spinal hypotension in preeclampsia.[6] This study showed no difference in pH, base excess, 1- and 5-min Apgar scores, or the number of neonates with an UA pH <7.2. There were significant differences between the two groups in terms of patient characteristics: gestational age and birth weight of the neonates, the indications for caesarean delivery, and the total equivalent doses of vasopressor. However, on multivariate regression analysis, a non-reassuring fetal heart tracing was the only variable associated with a low UA pH. By comparison, the patients in the present trial all had severe features of preeclampsia, and most had early onset disease, with a mean gestational age of 33 weeks.

A concern associated with our study was the necessity to obtain consent at short notice before the procedure; this was done in a sensitive and empathetic manner, and was also made easier by virtue of the straightforward intervention of the study. The small imbalance in sample size due to difficulties in obtaining umbilical arterial specimens in 3 cases, did not affect the estimated difference in the primary outcome.

Saravanan et al reported a potency ratio for equivalence between phenylephrine and ephedrine infusions of 80:1 in healthy women undergoing elective caesarean delivery after 36 weeks' gestation.[17] There is no data on the relevant potency difference in preterm severe preeclamptic patients. The ratio of the ephedrine to phenylephrine dose used in this study was based on our clinical experience of managing spinal hypotension in many similar cases; Figure 2 shows that the blood pressure control was similar in the two groups.

In conclusion, the important finding of this study is that fetal acid- base status is independent of whether phenylephrine or ephedrine is used as a bolus to treat spinal hypotension in patients with severe preeclampsia. The choice of vasopressor should be based upon maternal haemodynamic response in the individual case.

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Table 1. Patient Characteristics and Intra-operative Data

	Complete Cohort (n=129)	Ephedrine (n=32)	Phenylephrine (n=32)
Age, years [Mean (SD)]	26 (6)	24 (6)	26 (6)
BMI, $kg.m^{-2}$ [Mean (SD)]	30 (6)	29 (6)	32 (6)
Gravidity, median (range)	2 (1-5)	1 (1-5)	2 (1-5)
Parity, median (range)	0 (0-4)	0 (0-4)	1 (0-3)
$MgSO_4$ therapy (n)	115 (89%)	29 (90%)	31 (97%)
Hydralazine therapy (n)	58 (45%)	16 (50%)	17 (53%)
In labour (n)	25 (19%)	5 (15%)	9 (28%)
Baseline MAP, [Mean (SD)]	127(14)	128 (14)	128 (15)
SBP > 160 mmHg (n)	121 (94%)	30 (94%)	30 (94%)
Proteinuria 3-4 + (n)	98 (76%)	19 (60%)	28 (88%)
Gestational age, weeks [Mean (SD)]	32.7 (3.3)	33.0 (3.7)	33.6 (3.6)
Neonatal weight, g [Mean (SD)]	1676 (747)	1744 (787)	1988 (860)
Amniotic fluid index, abnormal (n)	10 (8%)	2 (6%)	0
UA doppler resistance index:			
No. with RI > 95^{th} percentile for gestational age	2 (1.5%)	0	0
No. with absent end diastolic flow	6 (5%)	1 (3%)	0
No. with reversed end diastolic flow	1 (0.8%)	1 (3%)	0
Placental weight, g [Mean (SD)]	380 (135)	392 (120)	420 (139)
TOTI, min	19 (6)	18 (5)	19 (5)
TIUI, min	12 (3)	12 (3)	12 (3)
TUID, sec	57 (42)	54 (29)	66 (64)
D-D interval, min	67 (33)	62 (23)	70 (32)
Nausea (n)	5 (4%)	1 (3%)	2 (6%)
Vomiting (n)	9 (7%)	5 (15%)	2 (6%)
Ephedrine pre-delivery, mg [median (range)]	n/a	15 (7.5 – 45)	n/a
Phenylephrine pre-delivery, µg [median (range)]	n/a	n/a	100 (50-650)

MAP – mean arterial pressure, SBP – systolic blood pressure, RI – resistance index, TOTI - time from arrival in theatre to induction of spinal anaesthesia, TIUI - time from induction of spinal anaesthesia to uterine incision, TUID - time from uterine incision to delivery, D-D - decision to delivery interval

Table 2. Blood gas data and neonatal outcome

Blood gas parameters	Entire cohort (n=133)	Ephedrine (n=32)	Phenylephrine (n=32)	Mean Difference	95% CI	P value
Neonatal umbilical arterial [mean (SD)]	Analysed: n=121	Analysed: n=31	Analysed: n=29			
pH	7.25 (0.09)	7.25 (0.08)	7.22 (0.10)	0.03	-0.02 to 0.08	.22
PCO_2 (kPa)	6.9 (1.37)	6.72 (1.29)	7.00 (1.58)	-0.28	-1.02 to 0.46	.45
PO_2 (kPa)	1.66 (0.7)	1.92 (0.78)	1.71 (0.76)	0.21	-0.19 to 0.62	.30
Base excess ($mmol.l^{-1}$)	-4.35 (4.08)	-4.81 (3.73)	-5.97 (4.60)	1.16	-1.00 to 3.32	.29
Standard bicarbonate ($mmol.l^{-1}$)	18.5 (3.06)	18.1 (3.02)	17.5 (3.48)	0.64	-1.04 to 2.32	.45
Lactate ($mmol.l^{-1}$)	3.56 (2.36)	3.76 (2.20)	3.82 (2.81)	-0.06	-1.37 to 1.25	.93
Neonatal umbilical venous [mean (SD)]	n=128	n=31	n=32			
pH	7.28 (0.08)	7.28 (0.07)	7.27 (0.10)	0.01	-0.03 to 0.06	.55
PCO_2 (kPa)	6.23 (1.3)	6.20 (1.24)	6.31 (1.34)	-0.11	-0.76 to 0.54	.74
PO_2 (kPa)	2.53 (0.73)	2.79 (0.68)	2.39 (0.62)	0.39	0.06 to 0.72	.02
Base excess ($mmol.l^{-1}$)	-4.84 (2.77)	-4.65 (3.89)	-5.36 (3.60)	0.72	-1.17 to 2.61	.45
Standard bicarbonate ($mmol.l^{-1}$)	19 (2.96)	18.9 (3.16)	18.2 (3.05)	0.64	-0.93 to 2.22	.42
Lactate ($mmol.l^{-1}$)	3.25 (2.29)	3.41 (2.18)	3.28 (2.44)	0.14	-1.04 to 1.32	.81
Maternal arterial [mean (SD)]	n=127	n=32	n=30			
pH	7.41 (0.03)	7.39 (0.04)	7.40 (0.03)	-0.01	-0.02 to 0.01	.57
PCO_2 (kPa)	4.07 (0.47)	4.11 (0.42)	3.94 (0.53)	0.17	-0.07 to 0.41	.17
PO_2 (kPa)	17 (5.94)	17.1 (5.07)	17.7 (6.62)	-0.60	-3.50 to 2.40	.71
Base excess ($mmol.l^{-1}$)	-4.84 (2.77)	-5.67 (2.57)	-6.05 (3.0)	0.38	-1.02 to 1.79	.59
Standard bicarbonate ($mmol.l^{-1}$)	20.8 (2.2)	20.1 (2.13)	19.9 (2.30)	0.30	-0.90 to 1.40	.64
Lactate ($mmol.l^{-1}$)	1.32 (0.56)	1.60 (0.53)	1.34 (0.55)	0.27	-0.01 to 0.54	.06
Neonatal Outcome	n=121	n=31	n=29			
UApH < 7.2 (n)	20/125 (16%)	6/31 (19%)	8/29 (28%)	-8.2%	-29.6 to 13.2%	.45
UA base excess >10 $mmol.l^{-1}$ (n)	11/125 (9%)	4/31 (13%)	4/29 (14%)	-1.0%	-18.1 to 16.3%	.92
1 min Apgar (median [range])	8 [2-10]	8 [4-10]	8 [4-9]			
1 min Apgar <7 (n)	41 (32%)	10 (31%)	12 (38%)	-6.3%	-29.5 to 17.0%	.60

5 min Apgar score (median [range])	9 [4-10]	9 [7-10]	9 [7-10]			
5 min Apgar <7 (n)	3 (2%)	0	0			
Intubation in OT (n)	0	1 (3%)	0			
Mortality prior to discharge from NICU (n)	3 (2%)	0	0			
IVH grade 3 or 4 (n)	3 (2%)	0	0			
HIE (n)	0	0	0			

UA – umbilical arterial, OT - operating theatre, NICU – neonatal intensive care unit,

IVH - intra-ventricular haemorrhage, HIE - hypoxic ischaemic encephalopathy

Figure 1: CONSORT Diagram

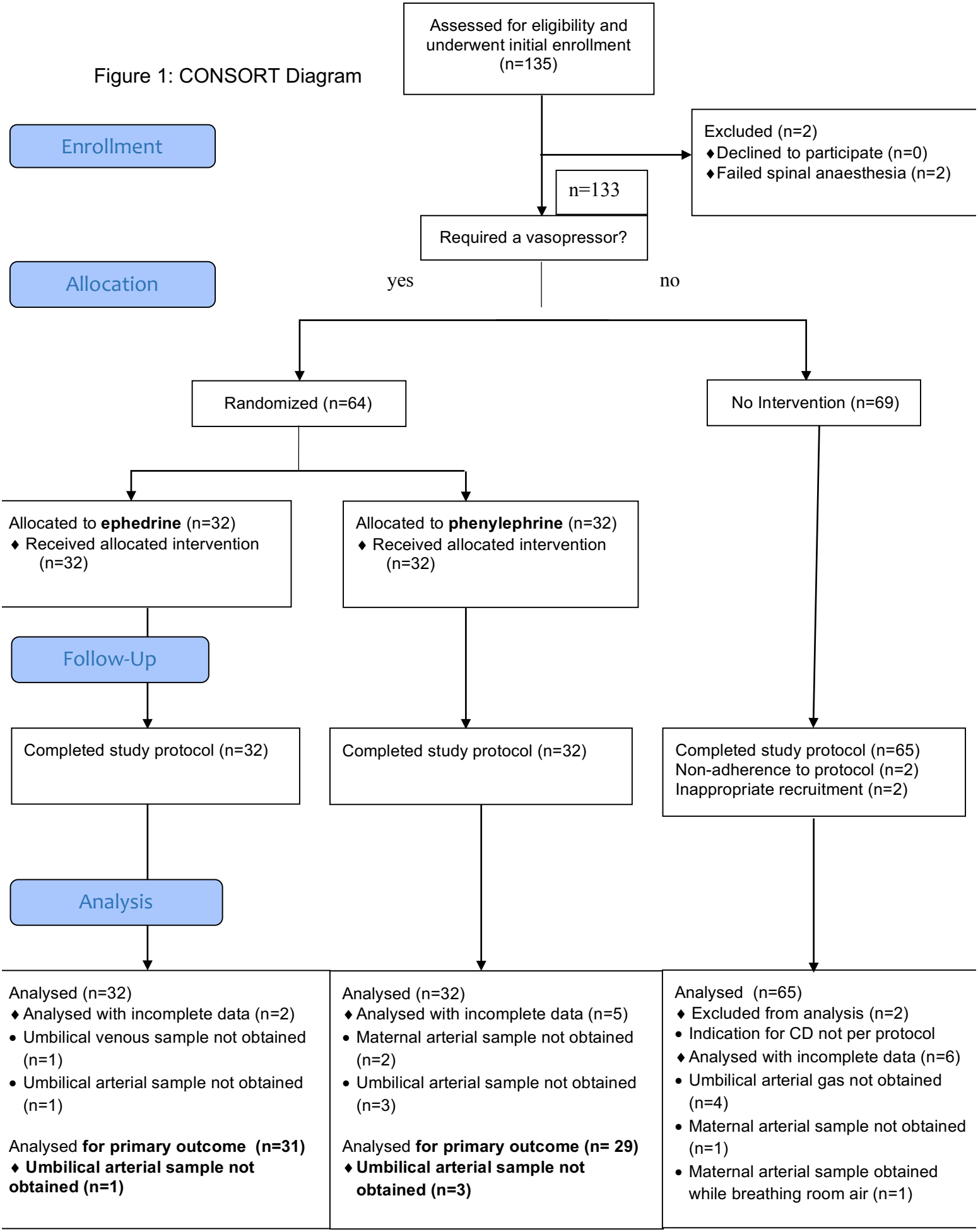


Figure 2: Non-parametric smoother (Lowess) of MAP over time by group

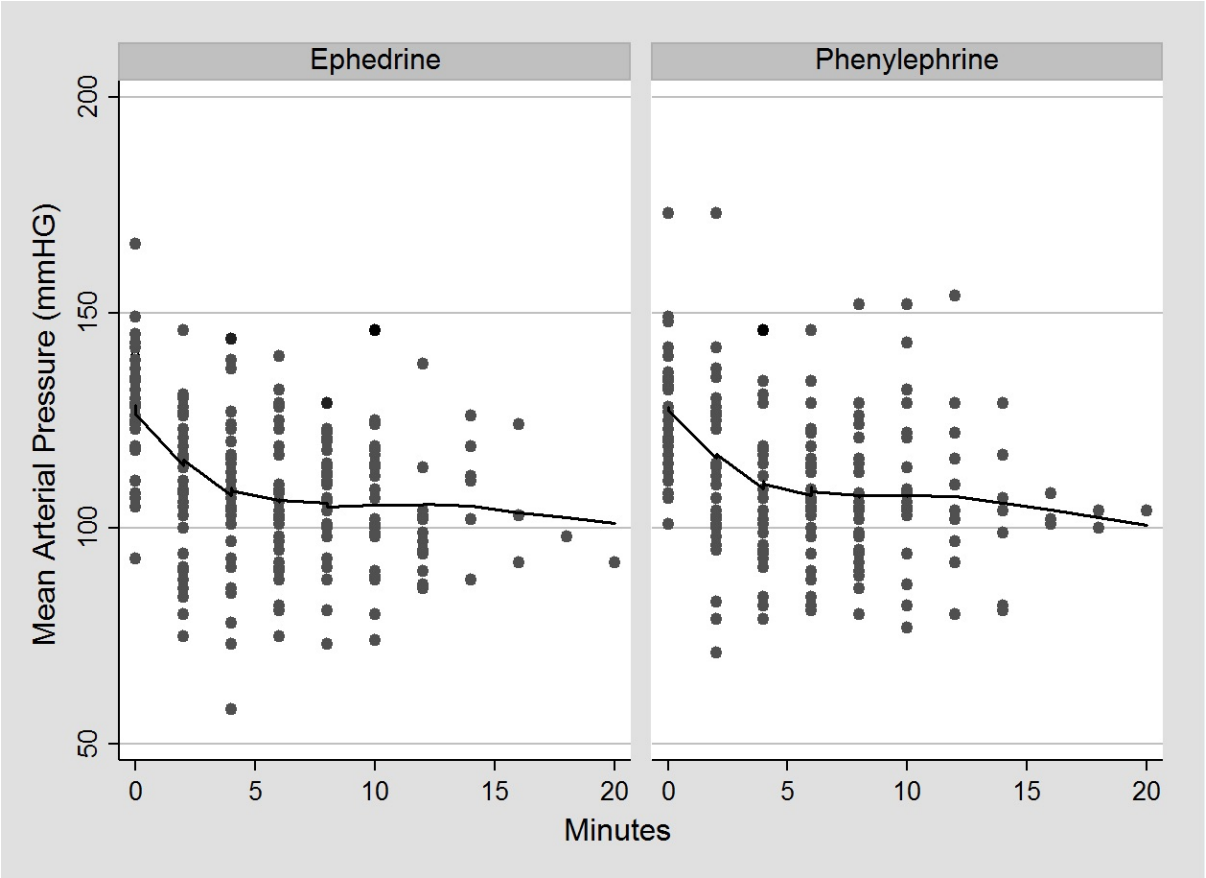
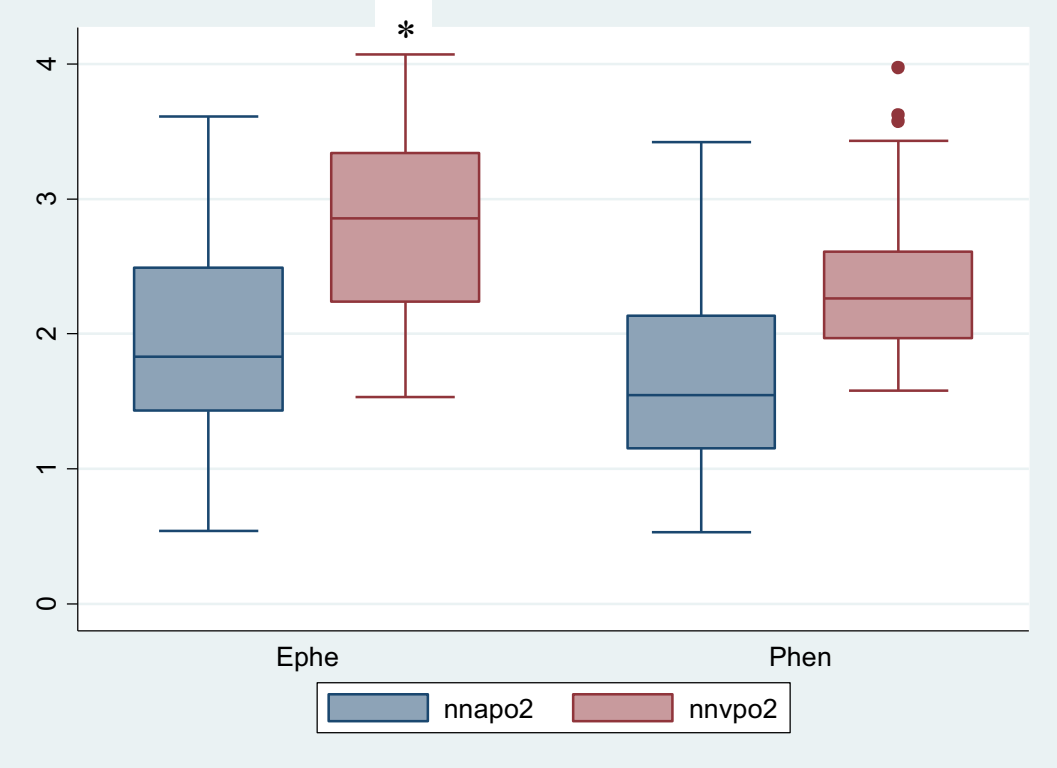


Figure 3: Comparison of umbilical arterial and venous PO_2 values



Box and whisker plot showing median, interquartile range, and range of values.
*Median neonatal venous PO_2 significantly higher in the ephedrine group
Ephe = Ephedrine; Phen = Phenylephrine

D: SUPPORTING DOCUMENTS
1.1 Letter of Approval from HSHREC

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

13 March 2015

HREC REF: 164/2015

Prof R Dyer
Anaesthesia
D23
NGSH

Dear Prof Dyer

PROJECT TITLE: A RANDOMISED COMPARISON OF BOLUS PHENYLEPHRINE AND EPHEDRINE FOR THE MANAGEMENT OF SPINAL HYPOTENSION IN PATIENTS WITH SEVERE PREECLAMPSIA AND A NON-REASSURING FETAL HEART TRACE (Sub-study linked to 040/2011) MMed Candidate - Ms S Adams

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

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 30th March 2016.

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.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

We acknowledge that the student, Samantha Adams will also be involved in this study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical

1.2 British Journal of Anaesthesia: Instructions to author

MANUSCRIPTS

For guidance, the requested size for articles is:

Clinical investigations: up to 3000 words and 30-40 references, 4-6 tables or figures.

Laboratory investigations: up to 3000 words and 30-40 references, 4-6 tables or figures.

Review Articles: up to 5000 words and 150 references.

Editorials: up to 2500 words and 25 references, 1 table or figure.

Case Reports: up to 1500 words and 15 references, 1 table or figure

Submissions which ignore this guidance on word count or number of figures/tables may be returned without being assessed. Authors wishing to submit manuscripts with figures/tables in excess of the recommended number should justify this in the submission letter.

For review articles and laboratory/clinical investigations it is possible to include supplementary data (such as additional references for a review, expanded tables of results or additional images for investigations) for on-line publication only. Authors should make clear in their submission letter which files are to be considered for on-line only publication.

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The British Journal of Anaesthesia welcomes case reports that illustrate new approaches to established clinical problems or describing a new problem. However, the acceptance rate for case reports is considerably lower than that for clinical studies. To be of value appropriate for publication a case report must provide a significant learning point for other anaesthetists. As a simple rule, just because a case is clinically challenging does not mean that it is appropriate to publish as a case report. To give an example, a case with a difficult airway and congenital heart disease who is managed using a recognized technique for a difficult airway and a recognized approach to managing the congenital heart defect, while being a clinical challenge, does not contain any learning points. Authors are referred to the editorial (British Journal of Anaesthesia 2008; 100 (6): 744) for further background to this subject.

The British Journal of Anaesthesia requires that permission is obtained from the patient or patient's relatives for submission of the case report for potential publication. This must be obtained before submission of the manuscript and the authors must state this in their submission letter. If photographs of the patient, in any form, are used a specific signed permission from the patient must be obtained and a copy of this submitted with the manuscript. Failure to comply with this will result in rejection of the manuscript.

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The British Journal of Anaesthesia welcomes review articles on clinical and scientific subjects. Authors are advised to contact the editor-in-chief before preparing or submitting a review to

ascertain the appropriateness of the subject for the journal and to prevent duplication of reviews which have been commissioned or published recently.

Reviews can be either narrative or systematic (see N. Webster; British Journal of Anaesthesia 2008; 100: 285-7).

Narrative reviews should cover all aspects of a subject and avoid being 'opinion' based. Narrative reviews should follow a logical structure but not in the Introduction, Methods, Results, Discussion format. The Summary should not be structured but should give a clear indication of the objectives and findings.

Systematic reviews can be presented in the Introduction, Methods, Results, Discussion format and with a structured Summary. The subject must be clearly defined. The objective of a systematic review should be to produce an evidence-based conclusion and if there are only few RCTs available (example only 3 small studies including a total of 120 patients) the value of the review will be very limited as the level of evidence is inadequate. The Methods should give a clear indication of the literature search strategy, data extraction, grading of evidence and analysis. (Example Evans, Lysakowski and Tramer British Journal of Anaesthesia 2008; 101: 610-7).

Co-publication of Cochrane reviews in the BJA

The BJA will publish reviews already published in the Cochrane Library if they meet the editorial standards. A condition for accepting co-publication of Cochrane reviews is that the publication has been accepted by the hosting Cochrane Review Group. The manuscript has to be rewritten to fit the BJA style and size limit of 5000 words. It is emphasized that results and conclusions of the review cannot be changed. The introduction must state that this is a co-publication of a Cochrane Review. The following should also be included:

1. The article title must end with the text 'a Cochrane Systematic Review'.
2. A footnote with the following text: '†This review is an abridged version of a Cochrane Review previously published in the Cochrane Database of Systematic Reviews xxxx, Issue xx, DOI: xxx (seewww.thecochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerge sand in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review.'

PREPARING YOUR MANUSCRIPT

The standard layout of a manuscript is:

• Title page
• Summary, including Keywords
• Introduction (not headed)
• Methods
• Results
• Discussion

• Details of authors contributions
• Acknowledgements
• Declaration of interests
• Funding
• List of references
• Tables (including legends to tables)
• Legends to illustrations

The pages should be numbered in the top right-hand corner, the title page being page one, etc. Start each section on a separate page.

TITLE PAGE

A separate page which includes the title of the paper. Titles should provide a reasonable indication of the contents of the paper. This is important as some search engines use the title for searches. Therefore, it is best to avoid enigmatic or vague titles such as 'An unusual cause of hypotension'. Titles in the form of a question, such as 'Is propofol epileptogenic?' may be acceptable.

The title page should include the name(s) and address(es) of all author(s). It should be made clear which address refers to which author. Details of the authors' qualifications and post (e.g., consultant, senior lecturer) are not required. An author's present address, if it differs from that at which the work was carried out, or special instructions concerning the address for correspondence, should be given as a footnote on the title page and referenced at the appropriate place in the author list by superscript numbers (1 2 3 etc.) If the address to which proofs should be sent is not that of the first author, clear instructions should be given in a covering note, not on the title page.

All authors should follow the criteria for 'authorship' as determined by International Committee of Medical Journal Editors. For details, please refer to section on British Journal of Anaesthesia Policies.

A short running title containing not more than 50 characters (including spaces) should be included.

SUMMARY (ABSTRACT)

The Summary (Abstract) will be printed at the beginning of the paper. It should be on a separate sheet, in structured format (Background; Methods; Results; and Conclusions) for all Clinical Investigations and Laboratory Investigations. For Reviews and Case Reports, the Abstract should not be structured.

The Abstract should give a succinct account of the study or contents, in up to 250 words. The Results section should contain data. It is important that the results and conclusion given in the Abstract are the same as in the whole article, as the Abstract may be used, as it stands, by abstracting journals. References are not included in this section.

KEYWORDS

Three to five keywords should be included on the summary page under the heading Keywords. They should be in alphabetical order and must be classified according to MESH keywords. These can be found here . Please note that UK English spelling will be used for these. Please do not simply list words you think are key. For example, propofol should be listed as: anaesthetics i.v., propofol;

TRIAL REGISTRY NUMBER

For Clinical Trials (also see below), please include the trial registry number under a separate heading after Keywords.

INTRODUCTION

The recommended structure for this section is;

• Background to the subject
• What is known / unknown about it
• What bit you are interested in / hypothesis
• Aim of your study

As a rule, the introduction to a paper should not require more than about 200 words and have a maximum of 1.5 pages double-spaced. The introduction should give a concise account of the background of the problem and the object of the investigation. It should state what is known of the problem to be studied at the time the study was started. Previous work should be quoted here but only if it has direct bearing on the present problem. For example, a description and evaluation of an analgesic infusion as part of an intravenous anaesthesia regimen need not include an exhaustive account of the previous literature addressing the problems of intravenous anaesthesia and the many studies of different analgesics, etc.

The final paragraph should clearly state the primary and, if applicable, secondary aims of the study.

If a preliminary account of the results has been given in a published abstract, it is customary to refer to this.

METHODS

The Methods section should give a clear but concise description of the process of the study. Subjects covered in this should include:

• Ethics approval / licence
• Patient population
• Inclusion / exclusion criteria
• Conduct of the study
• Data handling
• Statistics

• (CTA)

Ethics approval / licence

Regardless of the country of origin, all clinical investigators describing human research must abide by the Ethical Principles for Medical Research Involving Human Subjects outlined in the Declaration of Helsinki, and adopted in October 2000 by the World Medical Association. This document can be found at http://www.wma.net/en/30publications/10policies/b3/. Investigators are encouraged to read and follow the Declaration of Helsinki. Clinical studies that do not meet the Declaration of Helsinki criteria will be denied peer review. If published research is subsequently found to be non-compliant it will be withdrawn or retracted.

On the basis of the Declaration of Helsinki, the British Journal of Anaesthesia requires that all manuscripts reporting clinical research state in the first paragraph of the Methods section that:

• The study was approved by the appropriate Ethics authority.

• Written informed consent was obtained from all subjects, a legal surrogate, or the parents or legal guardians for minor subjects, or that the requirement for written informed consent was waived by the ethics committee.

Human subjects should not be identifiable. Do not disclose patients' names, initials, hospital numbers, dates of birth, or other protected healthcare information. Keep copies of ethics approval and written informed consents. In unusual circumstances the editors may request blinded copies of these documents to address questions about ethics approval and study conduct.

This section must include the Clinical Trials Authorization as all studies must be registered, as per the EU directive on clinical trials which came into force on 1st May 2004. There are a number of trial registration sites including EudraCT (http://eudract.emea.europa.eu) From January 2009 studies published in the British Journal of Anaesthesia must include the trial registration number in the Methods.

Example; The study was approved by the X regional research ethics committee (Ref: 07/A123/456) and registered with EudraCT (ref: 2007:123456:AA).

For more details about Clinical Trials, please see section below.

The title of this section should be 'Methods'. 'Materials and methods' or 'Patients and methods' should not be used. While brevity is essential, the methods must be described in sufficient detail to allow the experiment to be interpreted, and repeated if necessary, by the reader. Previously documented standard methods need not be recounted in detail, but appropriate reference to the original should be cited. Where the programme of research is complex such as might occur in a cardiovascular study in animals, it may be preferable to provide a table or figure to illustrate the plan of the experiment, thus avoiding a lengthy explanation.

Sometimes detailed laboratory techniques may be filed separately in a recognized library and a note to this effect given in the manuscript. Where measurements are made, an indication of the

error of the method in the hands of the author should be given. The name of the manufacturer of instruments used for measurement should be given with an appropriate catalogue number or instrument identification (e.g. Radiometer PHM 7). The manufacturer's town and country must be provided. In the case of solutions for laboratory use, the methods of preparation and precise concentration should be stated.

DRUGS

When a drug is first mentioned, it should be given by the international non-proprietary name, followed by the chemical formula in parentheses if the structure is not well known, and (if relevant) by the proprietary name (with an initial capital letter). A figure giving the molecular configuration of the drug is necessary only in the case of the earliest reports of a new drug. The author should indicate in an accompanying note to the editor the source from which he has obtained the molecular configuration; it is an important requirement that the author should check the accuracy of the configuration in every detail. Drug dosages are normally given by the name of the drug followed by the dose (e.g. propofol 2.5 mg kg -1). Do not confuse drug dose with concentration.

MULTIPLE PUBLICATIONS OF HUMAN OR ANIMAL TRIALS

In the interest of minimizing the risk to human and animal subjects, as well as promoting efficient use of scarce research funds, investigators will sometimes pose several questions and make multiple measurements in a single study, with the intent of publishing multiple manuscripts. This may be a laudable practice, or it may be an inappropriate attempt to slice a single study into 'minimum publishable units'. Division of data from a single research study into multiple manuscripts is acceptable, provided three requirements are met:

1. The cover letter for every paper derived from the study explains the need for dividing the study into multiple manuscripts. This applies even if only one of the submissions is to the British Journal of Anaesthesia . It is essential that the cover letter states that other parts of the study are currently under consideration or in press with another journal. The Journal will consider the appropriateness of the division as part of the review process.
2. In all manuscripts after the first, the investigator must disclose that the subjects reported in the study have been previously reported, with appropriate citation to the first manuscript. This practice is essential for scientific continuity. For example, should a question arise about the conduct of the study in one manuscript, readers should be able to identify all manuscripts based on the same experimental data.
3. Measurements must not interfere with each other. Such interference may happen in ways that are not evident at the time of the study. For example, measurements of pain thresholds may make it impossible to measure sedative effects. The potential for interfering measurements may not be evident if the pain thresholds and sedation effects are reported in separate manuscripts that are not appropriately cross-referenced.

PATIENTS

Data on the mean age (range), weight, sex, height, criteria for selection, etc. (patient characteristics, not demographics) should be presented, with an indication of the general state of health and type of operation being undertaken. Animal data on sex, strain and weight should be included. Although it is usually possible to make such a statement in a short paragraph, more complex information may be preferable as a table. However, tables and figures are expensive to produce and should not be used unnecessarily. Where it has been necessary to seek permission from the patients for the type of study being undertaken, this should be indicated.

CLINICAL TRIALS

In accordance with the Clinical Trial Registration Statement from the International Committee of Medical Journal Editors (see here), all clinical trials in British Journal of Anaesthesia must be registered in a public trials registry at or before the onset of participant enrollment. This requirement applies to all clinical trials that begin enrollment after 1 January 2009. For trials that began enrollment before 1 January 2009, registration is strongly recommended and if the trial reported was not registered, please comment on this matter in the covering letter.

Research is considered to be a clinical trial if it involves prospective assignment of human subjects to an intervention or comparison group to study the relation between a health-related intervention and a health outcome. Further details of which clinical trials are covered by this policy are in the updated ICMJE guidelines available here.

The registry must be accessible to the public at no charge, searchable, open to all prospective registrants, and managed by a not-for-profit organization. The registry must include the following information: a unique identifying number, a statement of the intervention(s), study hypothesis, definition of primary and secondary outcome measurements, eligibility criteria, target number of subjects, funding source, contact information for the principal investigator, and key dates (registration date, start date, and completion date). The following registries are recommended by ICMJE: Clinical Trials, ISRCTN Register, UMIN Clinical Trials Registry, Australia New Zealand Clinical Trials Registry, Nederlands Trial Register.

In accordance with the ICMJE's recommendation, British Journal of Anaesthesia will also accept registration of clinical trials in any of the primary registers that participate in the World Health Organization's International Clinical Trial Registry Platform (see here). Primary registers are WHO selected registers managed by not-for-profit entities that will accept registrations for any interventional trials, delete duplicate entries from their own register, and provide data directly to the WHO. Please note that registration in any WHO partner register is insufficient.

Authors are requested to provide the exact URL and unique identification number for the trial registration at the time of submission. This information will be published in the article and we ask that you include the URL and identification number on the title page of your manuscript.

Clinical trial reports should also comply with the Consolidated Standards of Reporting Trials (CONSORT) and include a flow diagram presenting the enrollment, intervention allocation, follow-up, and data analysis with number of subjects for each (see here). Please also refer specifically to the CONSORT Checklist of items to include when reporting a randomized clinical trial.

Results posted in the same clinical trials registry in which the primary registration resides will not be considered prior publication if they are presented in the form of a brief abstract (500 words or less) or a table.

RESEARCH USING ANIMALS

Institutional approval

Studies that involve the use of animals must clearly indicate that Institutional approval was obtained and state the UK Home Office Licence number or local equivalent that the studies were performed under. It is recognized that animal welfare legislation can vary between countries and so the BJA uses the UK standards as a baseline and reserves the right to reject manuscripts judged not to meet these standards, even when local approval has been granted.

Anaesthesia

The methods of anaesthesia and analgesia for research studies involving animals should be the best available to ensure the welfare of the animals involved. Reducing the potential for pain and distress is a significant refinement and provision of safe and effective anaesthesia that does not interfere with specific research objectives also reduces the numbers of animals used. Authors must also state how they assessed and monitored the adequacy of anaesthesia.

Some anaesthetics may have interactions that are important to certain areas of research. For example medetomidine and xylazine both cause hyperglycaemia, osmotic diuresis, and effects on the cardiovascular system. When used in conjunction with ketamine, these agents both produce surgical anaesthesia in rodents, suitable for a range of different operative procedures. However the side-effects may make them unsuitable for certain types of research. The safe dose of intra-peritoneal pentobarbital in rats has a narrow range and unpredictable duration; indeed a larger dose is often used for killing an animal at the end of a procedure. Whichever agent is used, an appropriate plane of anaesthesia for the intervention must be assessed and achieved. This is particularly important when neuromuscular blocking agents are used.

Information on potentially suitable anaesthetic regimens can be obtained from a variety of sources, including the veterinary advisor at your research institution, specialist laboratory animal anaesthesia and general veterinary anaesthesia textbooks. Obtaining information on potential interactions with research procedures is less easy to obtain and frequently requires a careful literature search. The agents available and the techniques for their administration are evolving so selecting the method used in other scientific publications will not guarantee the most appropriate method. The choice of anaesthetic and route of administration should:

• Provide the required depth and duration of anaesthesia for the procedure
• Be simple to administer, without distress to the animal
• Should be free from undesirable side effects and allow uncomplicated recovery
• Should cause the minimum of interference with the purpose of the research procedure

Analgesia

When animals are used in biomedical research, every effort should be made to minimise any pain or distress. Not only is this important for ethical reasons, but also because pain is a source of stress that can cause undesirable effects on the outcome of research projects. Considerable progress has been made over the last 10-15 years in preventing or alleviating pain. In particular, there is now considerable opportunity to minimise or eliminate pain following surgical procedures. A wide range of analgesics are available, and it is a simple process to administer one of these agents to prevent or alleviate postoperative pain. It is also important to:

• Administer an appropriate analgesic that provides the required intensity of pain relief
• Administer the analgesic at an appropriate dose
• Continue its administration at appropriate time intervals
• Stop administering the analgesic at an appropriate time after surgery

Provision of effective pain relief requires that all of these points are addressed, but this can only be done by assessing the degree of pain experienced by the animal involved. Animal pain assessment is difficult and time-consuming to implement effectively, so that it is tempting to simply give all animals a "standard dose" of analgesic. In man, the use of such fixed dose regimens has been identified as one of the factors contributing to inadequate pain management, so this approach should be avoided when dealing with laboratory animals.

In humans, analgesic dose rates are based on clinical trials, using well-established methods of assessing pain. In animals, we are unable to assess the severity of many types of pain accurately. Often, all that is possible is to use dose rates that have been established to be safe and effective in some of the tests used in rodents during early drug development. Provided these limitations are appreciated, there are some strategies for pain management which make best use of our existing knowledge:

• If methods of pain assessment have been developed for the species used, then these should be adapted to the requirements of the particular research procedure being undertaken
• If methods of pain assessment are not available, consider devoting resources to developing some form of scoring system
• If pain scoring is not possible, determine the analgesic protocol based on clinical experience with other surgical procedures in that species
• If possible, use dose rates that have been established using studies that have employed pain scoring systems
• Use pre-emptive analgesia and consider using several analgesic agents

• Attempt to evaluate the efficacy of the analgesic regimen selected using clinical assessment (your veterinary advisor will be able to help you to recognise pain in laboratory animals)
• Prepare a rescue analgesia protocol and an immediate euthanasia protocol for animals which appear to be in severe pain

The use of animal models of pain to investigate analgesia techniques is a particular minefield for journals in the field of anaesthesia. Such studies must be conducted with extremely careful regard to animal welfare. Rarely will this journal publish studies where an analgesic agent has been compared to a placebo in an animal model of severe pain.

The book 'Laboratory animal anaesthesia' by Professor Paul Flecknell (3rd Edition, 2009, Academic Press) provides a very helpful introduction for research workers for safe, effective and appropriate anaesthesia and analgesia in animals used in research studies.

Euthanasia

Euthanasia is defined as a pain-free or stress-free death and animals used for research are usually euthanized at the end of a study for the purpose of sample collection or post-mortem examination. Animals may also be killed because they are experiencing severe pain or distress. The method of killing the animal after the experiment is completed should be chosen carefully and must be detailed in manuscripts. The method used should be appropriate to the species and the method used should not confound any objective of the research - veterinary advice should be sought. The conduct of euthanasia for those working with laboratory animals in the UK is quite straightforward. Either the Code of Practice for the Humane Killing of Animals under Schedule 1 to the Animals (Scientific Procedures) Act 1986 is followed or a project and personal licence authorisation is obtained to use a technique not covered by this Code. An updated code of practice for schedule 1 killing has been published by the Animal Procedures Committee and is available online at:

http://apc.homeoffice.gov.uk/reference/schedule-1-report.pdf

The use of carbon dioxide for killing is a subject of much debate and is not suitable for rabbits. For rodents, the use of carbon dioxide is still permitted but other methods are preferable. When carbon dioxide is used, do not pre-fill the cage or chamber with carbon dioxide and use slow filling rates to minimise discomfort. The flow rate can be increased when the animal is unconscious.

ARRIVE guidelines

The contribution of animal research in enabling better health for man and animals is incontrovertible and the BJA is committed to the publication of research studies which use animal models, but demands the same rigorous attention to detail as in clinical trials. Failure to describe research methods and to report results appropriately has scientific and ethical implications for the entire research process and the reputation of those involved in it.

Experiments involving animals should be appropriately designed, correctly analysed and then transparently reported, to both increase the validity of the results, and maximise the scientific gain. A minimum amount of relevant information must be included in manuscripts published in this journal to ensure that the methods and results of a study can be reviewed, analysed and repeated. The BJA will therefore refer to the ARRIVE (Animals in Research: Reporting In Vivo Experiments) guidelines as the basis for the process of reviewing manuscripts of research involving animals.

These guidelines were generated by The National Centre for the Replacement, Refinement and Reduction of Animals in Research, which is an independent scientific organisation, established by the UK Government, in consultation with scientists, statisticians, journal editors and research funders.

ANAESTHESIA

Descriptions of methods of anaesthesia are often unnecessarily cumbersome. The following model is presented as an example of economy of words: The patients did not receive premedication. Anaesthesia was induced with propofol 2 mg kg -1 and fentanyl 1.5 μg kg -1 . Vecuronium 0.1 mg kg -1 was given to facilitate orotracheal intubation with a cuffed tube. Anaesthesia was maintained with sevoflurane 1.5-2.0% and nitrous oxide 60% in oxygen, with positive pressure ventilation in a circle system. A similar description should be used for animal anaesthesia.

STATISTICAL ANALYSIS

Statistical methods must be described with enough detail to enable a knowledgeable reader with access to the original data to verify the report and results. Where possible, findings should be quantified and presented with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Confidence intervals provide a more informative way to deal with a significance test than a simple P value. A power analysis should be performed before starting the study to determine the number of subjects which need to be studied in each group to detect a given change. Please note that a power analysis based on the primary end-point will not necessarily be applicable to any secondary measures.

It is recommended that authors seek appropriate statistical advice before starting their study, to ensure that the structure and planned recruitment is adequate to answer the question set.

RESULTS

Guidance for this section includes;

• Must be factual
• Relate to aims
• Logical order
• State significances
• Negative findings

From January 2009, all randomized control trials (RCTs) must adhere to the Consort guidelines and present a flow diagram which details the conduct of the study (http://www.consort-statement.org/)

Description of experimental results should be concise. They should be presented in a factual manner and related to the aim of the study. It is often useful to present the results in the order described in the Methods section. Data should not be repeated unnecessarily in text, tables and figures (see below), and unwarranted numbers of digits should be avoided (Example: the mean dose of propofol was 2.1 mg kg -1 rather than 2.0897 mg kg -1). It may not be necessary to provide all the data from a complex study: only those values which are essential to the communication should be given. However, results should be presented in a manner so that the reader can check the statistical inferences. If the data are so numerous that this is not possible, the editor must be sent a full set with the submission of the original manuscript and the readers should be informed as to where they can obtain a similar full set of results. Where appropriate, for example in a pharmacokinetic study, more extensive sets of data can be included as an appendix with the on-line version of the article. If authors wish to make use of this facility, they should state this in the submission letter and upload the data as a separate file. The editor has the right to request the original data collected. In the results section there should be no attempt at a discussion of the findings.

TABLES AND FIGURES

Figures and Tables are often useful to present either complex or extensive data in a more easily understandable form. However, authors are cautioned against unnecessary use of tables and figures. A useful approach is to prepare the raw data in the form of tables and then decide which data are to be presented in the article. The author should then decide whether the essential data be presented succinctly in the text. If not, the essential tables/ figures should be prepared. To illustrate this with examples: a study outcome which compares two measurements in two groups can easily be presented as text, a comparison of arterial pressure and heart rate changes at five timepoints in two groups would be appropriate as a table and the same measurements in comparing three groups may be better as a figure.

Tables and figures are important communications and should be accompanied by a legend which makes it self-explanatory. However, the legend must not contain experimental details, which should be given in the methods section.

The use of a figure should be considered only where a figure will present the data more clearly than is possible in a table or when an important trend or comparison has to be made for which a graphic presentation is clearly superior to a table or text.

The authors should decide which form they wish to present data in. Please note the limitation given above on the number of figures/tables permissible for each article type. Duplication of data by including it as a table and as a figure is unnecessary and wasteful.

Authors are advised to note the limitation on the number of figures/tables given above (4-6 tables or figures, in total) for clinical and laboratory investigations and 1 figure or table for a case report or editorial. The use of multiple small figures submitted as one figure (for example Figure 1 a-f) is discouraged as when reduced to printed size these may not be clear. Authors are strongly advised to be selective in their use of figures and tables.

For further guidance on the format of tables and figures, see below. It is recommended that the author refers to previous issues of the journal regarding appropriate style.

DISCUSSION

This is an important part of the manuscript but it should not be too long, perhaps one third of the total length of the paper. This requires discipline by the author for two reasons: first, they may feel that the task is nearly completed and that they are subject to fewer constraints; second, many authors seem to wish to read into their data more than is actually there.

It is suggested that the discussion should normally follow the pattern below:

• State main findings
• How do they fit in with previous studies
• Why are they different / same
• What it adds to knowledge of subject
• Weaknesses in study
• Future studies
• Conclusions

State main findings

This does not mean a repetition of all the results with their statistics. It should provide a concise overview of the study. For example, ' Drug X produced a greater haemodynamic change on induction of anaesthesia than occurred with drug Y, resulting in a greater fall in arterial pressure and a higher incidence of tachycardia '.

How do they fit in with previous studies

This section should relate directly to the statements made in the Introduction and qualify you finding in relation to the previous studies of the subject. For example, mention any important uncertainties in the methods of measurement. In laboratory studies, try to relate the concentrations used to those encountered clinically.

Why are they different / same

Deductions which may explain important differences between the data of the present study, and the data of previous studies. The author should avoid excessive speculation in this section. It is quite reasonable to suggest possible explanations for your findings and any differences from previous studies but the 'missing parts' of such reasoning must be acknowledged.

What it adds to knowledge of subject

This can summarise the previous sections by pulling together the implications of your main

findings, studies by other workers and their combined contribution to our knowledge of the subject. This should not be just another repetition of the results and preceding discussion but more of an expanded conclusion.

Weaknesses in study

It is appropriate to briefly acknowledge any limitations of your study at this point. Examples here could include the patient population, limitations of analytical tests, patients lost to follow-up. Authors are advised to be honest but succinct in this section.

Future studies

A logical follow on to the two previous sections is to identify future studies that would address some of the potential explanations and limitations discussed earlier. This should again be concise. An extensive list of future studies undermines you own study: i.e. has it answered anything if there are still so many questions?

Conclusions

Conclusions from the present study. The original contribution to knowledge from the present study is stated. A common fault here is to overstate the findings from a study. For example, if you have studied the effect of a new drug in an animal model you cannot draw any conclusions at all about its effect in humans and likewise if you studied ASA 1 and 2 patients you cannot comment on its use in critically ill patients.

It may be appropriate to give the implications of the conclusions for anaesthetic practice and the indications for further enquiry in this area of interest.

Authors should remember at all times, but especially in writing the discussion, that they will spoil their manuscript by excessive length. A discussion of more than three pages is often too long.

DECLARATION OF INTERESTS

It is essential to acknowledge all sources of financial assistance, and any potential material benefit expected from publication of the work. Also, please describe the role of the study sponsor, if any, in study design; collection, analysis and interpretation of data; writing the report; and the decision to submit the report for publication.

Each manuscript must contain a declaration of interests from ALL authors. This should include all possible interests in the past five years. This is obviously most common in studies involving new equipment or drugs, but other areas such as advisory bodies are also relevant.

For example: 'Dr A has received an honorarium from Company X. Dr B has received a travel grant from Company Y. Prof C is a member of the national advisory committee on Z.'

You are required to declare all authors' interests at the time of submitting your manuscript by completing and uploading a conflict of interest form. Please upload it as a separate file labelled “conflict of interest form” along with your manuscript. Please make sure that all authors have signed before uploading, even if there are no interests to be declared.

FUNDING

Details of all funding sources for the work in question should be given in a separate section entitled 'Funding'. This should appear before the 'Acknowledgements' section.

The following rules should be followed:

The sentence should begin: 'This work was supported by …'

The full official funding agency name should be given (one of the 27 subinstitutions), i.e 'National Institute for Academic Anaesthesia', not 'NIAA' or 'NCI at NIH' (full RIN-approved list of UK funding agencies)

Grant numbers should be complete and accurate and provided in brackets as follows: '[grant number ABX CDXXXXXX]'

Multiple grant numbers should be separated by a comma as follows: '[grant numbers ABX CDXXXXXX, EFX GHXXXXXX]'

Agencies should be separated by a semi-colon (plus 'and' before the last funding agency)

Where individuals need to be specified for certain sources of funding the following text should be added after the relevant agency or grant number 'to [author initials]'.

An example is given here: ' This study was funded by a small project grant from The Royal College of Anaesthetists (07/123) (AB). Equipment was provided by a project grant from British Journal of Anaesthesia/RCoA (06/321) (CD) .'

Oxford Journals will deposit all NIH-funded articles in PubMed Central. See http://www.oxfordjournals.org/for_authors/repositories.html for details. Authors must ensure that manuscripts are clearly indicated as NIH-funded using the guidelines above.

AUTHORS' CONTRIBUTIONS AND AUTHORSHIP

All manuscripts submitted to BJA must inform the readers of individual contribution which each author made to the research and/or manuscript.

Please give initials of the names of each of the authors (i.e. R.D., I.K.M.) , and against their initials list the contributions which they individually made to the work (i.e. R.D. : Study design and data analysis; I.K.M.: Patient recruitment, data collection and writing up of the first draft of the paper).

Each author must take responsibility for at least one component of the work, should be able to identify who is responsible for each other component, and should ideally be confident in their co-authors' ability and integrity.

The British Journal of Anaesthesia follows recommendations of International Committee of Medical Journal Editors (ICMJE). To comply with ICMJE recommendations, all the authors must meet all of the following four conditions:

- substantial contribution to conception and design, acquisition of data, or analysis and interpretation of data;

- drafting the article or revising it critically for important intellectual content;
- final approval of the version to be published; and
- agreement to be accountable for all aspects of the work thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

For large, multicentre studies, the group of investigators should identify individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship.

If the author list includes a group name all members of the group must meet the full criteria and requirements for authorship as described above. If all members of a group do not meet all authorship criteria, a group must designate one or more individuals as authors or members of a writing group who meet full authorship criteria and requirements. Other group members who are not authors may be listed as Collaborators (sometimes called non-author contributors) in an Appendix. PubMed will list the names of individual group members who are authors or collaborators. There should be a note associated with the byline clearly stating that the individual names are elsewhere in the paper and whether those names are authors or collaborators. Collaborator names are searchable on PubMed in the same way as authors. PubMed rules for this can be found here.

ACKNOWLEDGEMENTS

The contributors, who do not meet the criteria for authorship, as determined by International Committee of Medical Journal Editors and given in the section on BJA Policies, should be listed in acknowledgements section. You may acknowledge the contributors, who do not justify authorship, under headings such as 'clinical investigators', 'participating investigators', 'served as scientific advisors', 'critically reviewed the proposal', 'collected data', or 'provided care for study patients'.

REFERENCES

Except for review articles, long lists of references are usually inappropriate. Restrict references to those that have direct bearing on the work described and cite only references to books and articles published in Index Medicus and Index Veterinarius journals.

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