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Webb, Adrian Arthur

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RE-EVALUATION OF THE ROLE OF INTRAMUSCULAR EPHEDRINE AS PROPHYLAXIS AGAINST HYPOTENSION ASSOCIATED WITH SPINAL ANAESTHESIA FOR CAESAREAN SECTION.

ADRIAN ARTHUR WEBB

A research report submitted to the Faculty of Medicine, University of Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Anaesthesia.

Johannesburg 1997.

DECLARATION

I hereby declare that this research is my own work. It has not been submitted for any degree or examination in any other University.

The research protocol was approved by the Committee for Research on Human Subjects (Medical), University of the Witwatersrand, Johannesburg. (Clearance certificate number M 960244.)



Adrian Arthur Webb

20th Day of February 1997.

DEDICATION

To my wife, Dianne

and my children Michael, Julianne and Angie.

ABSTRACT

Spinal anaesthesia for Caesarean section is associated with an unacceptably high incidence of hypotension despite the administration of an intravenous fluid preload and the use of uterine displacement. The theoretical benefits of preventing hypotension as opposed to treating it as it occurs are the avoidance of considerable maternal discomfort, a reduced risk of serious cardiovascular or respiratory depression and the avoidance of transient foetal asphyxia.

The use of prophylactic intramuscular ephedrine prior to spinal anaesthesia has been recommended but not well studied. The advantages of the intramuscular route for ephedrine administration are its simplicity and its favourable pharmacokinetic profile. Cardiovascular support is sustained throughout the surgery and into the post operative period. Opposition to the use of intramuscular ephedrine in the prevention of hypotension is based on two studies in which spinal anaesthesia was not used [1,2]. These studies showed an unacceptably high incidence of hypertension, a deleterious effect on foetal gas exchange and a lack of efficacy when intramuscular ephedrine was used in epidural and general anaesthesia respectively.

This research report describes a randomised, double blind, interventional study designed to assess the safety (prevalence of hypertension, tachycardia or foetal compromise) and efficacy (prevalence of hypotension) of 37,5mg of ephedrine given prior to spinal anaesthesia for Caesarean section. Forty patients who had given informed consent were entered into the study. Blood pressures and pulse rates were recorded for 90 minutes after ephedrine administration, samples of umbilical venous blood were collected and Apgar scores assessed.

This study found that giving 37,5mg of intramuscular ephedrine prior to spinal anaesthesia was safe from a maternal point of view in that it was not associated with reactive hypertension or tachycardia. When the ephedrine was given 10 minutes prior to induction of the spinal the technique proved to be effective in reducing the incidence and severity of hypotension. When used in the above manner the technique was not associated with foetal depression or acidosis.

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LIST OF ABBREVIATIONS

ASA	American Society of Anesthesiologists
COMT	Catechol-o-methyl-transferase
MAO	Monoamine oxidase
T2	Thoracic dermatome level 2
L2	Lumbar dermatome level 2
sd	Standard deviation
t	A numerical value determined by the Student's t-test
P	The probability that a difference could be explained by chance

CHAPTER 1

INTRODUCTION

1.1 BACKGROUND TO THE USE OF INTRAMUSCULAR EPHEDRINE IN SPINAL ANAESTHESIA

The use of spinal anaesthesia for obstetrical procedures dates back to 1901 but it was only in the 1940's that use of the technique became widespread [3]. Although spinal anaesthesia was used extensively for Caesarean sections until the late 1960s, associated complications including hypotension and post dural puncture headache led to a decline in its use in favour of epidural anaesthesia. It is only recently that spinal anaesthesia has enjoyed a resurgence of popularity in the obstetrical anaesthesia world and this relates to the development of small gauge needles and newer bevel designs.

Ephedrine was first used to treat and prevent post-spinal hypotension in 1927 [4]. The use of prophylactic intramuscular vasopressors prior to spinal anaesthesia became widely practised in the1950's [5]. However a prospective study published in 1960 detected an association between the use of intramuscular vasopressors and severe postpartum hypertension [6]. The study had been prompted by the occurrence of an intracranial haemorrhage two hours postpartum in a patient who had received a prophylactic vasoconstrictor prior to caudal anaesthesia. This finding, and a widely quoted study by Wollman in 1968 which purported to show the success of fluid preloading in preventing hypotension, led to a decrease in the use of prophylactic vasopressors [7].

In a review article in Anesthesiology in 1970, Smith and Corbascio declared the "decline and fall of the vasopressor" and warned of the danger of injudicious use of these drugs [8]. A move towards more physiological methods to control blood pressure under anaesthesia was encouraged.

However, in spite of an increased understanding of the pathophysiology of spinal anaesthesia and the use of conservative physiological methods (intravenous fluids and left lateral position), the incidence of post-spinal hypotension remained unacceptably

high. Wollman's results were not borne out by subsequent studies and the focus returned to vasopressors for the prevention and treatment of post spinal hypotension. The question became, not whether to use vasopressors, but how to use them. The continuing contention revolves around whether to use the vasopressors on a prophylactic or therapeutic basis .

Proponents of the prophylactic approach argue that allowing a rapid precipitous fall in blood pressure has significant clinical consequences i.e.foetal asphyxia, considerable patient discomfort with nausea and vomiting and the potential for respiratory depression and electromechanical dissociation [9-11]. On the other hand opponents of the prophylactic approach criticise the unnecessary administration of vasoactive drugs which in some cases would constitute overtreatment. They cite maternal hypertension and tachycardia and foetal asphyxia relating to uterine artery vasoconstriction as potentially harmful side effects [1,2].

In 1976, in a widely quoted study of a small sample of patients, Gutsche demonstrated the efficacy of combining the physiological methods of intravenous fluid preload and left lateral tilt with the pharmacological method of prophylactic intramuscular ephedrine [9]. Although this technique continues to be recommended by contemporary text books of obstetrical anaesthesia [12], considerable prejudice has developed against the use of intramuscular ephedrine in neuraxial anaesthesia in pregnancy because of concerns raised by two studies.

The first, in 1982 by Rolbin et al, showed a high incidence of reactive hypertension when intramuscular ephedrine was used in an epidural context [1]. It should be noted that inferences about the cardiovascular effects of intramuscular ephedrine in spinal anaesthesia should not be made from a study of epidural anaesthesia as the two techniques are physiologically and pharmacologically different.

The other more recent study to criticise intramuscular ephedrine in obstetrical spinal anaesthesia was published in 1992 by Rout et al [2]. They emphasised the problem of failing to administer the spinal after giving intramuscular ephedrine and then having to convert to general anaesthesia where subsequent reactive hypertension may be

problematic. Rout et al, not surprisingly, demonstrated reactive hypertension in patients given intramuscular ephedrine who received a general, not a spinal, anaesthetic. On the basis of this and because they detected statistically significant (but clinically insignificant) acid base changes in umbilical cord blood, they unequivocally condemned the use of intramuscular ephedrine in obstetrical spinal anaesthesia.

This study has been designed to assess whether concerns raised by the above studies on intramuscular ephedrine apply to the now revived technique of spinal anaesthesia for Caesarean section.

The preferred route of ephedrine administration in South Africa is the intravenous one. Intravenous methods could be categorised as prophylactic, early therapeutic or late therapeutic. Prophylactic methods comprise either an intravenous bolus directly after the spinal is induced or a continuous intravenous infusion titrated to systolic blood pressure also commenced after induction of the spinal anaesthetic [10]. Early therapeutic intravenous treatment implies a small bolus dose as soon as blood pressure declines as opposed to the late therapeutic method where an ephedrine bolus is only given when systolic blood pressure declines below 100mmHg or by more than 30% [11].

The disadvantage of the intravenous infusion method relates to its demands in terms of effort and equipment particularly in a less sophisticated environment where patient turnover is high. The disadvantage of the intravenous bolus method lies in the short duration of action of ephedrine which mandates repeated boluses and frequent and prolonged blood pressure monitoring. A recent case report of a cardiac arrest after Caesarean section under subarachnoid anaesthesia was causally related to an episode of post-operative hypotension [13]. In this instance intravenous boluses of ephedrine had been used intra-operatively.

The candidate sees theoretical advantage in the intramuscular route for ephedrine administration over the intravenous one in its simplicity and its potentially favourable pharmacokinetic profile i.e. prolonged uptake results in plasma levels of ephedrine being maintained throughout the intraoperative and into the post operative period providing sustained and reliable cardiovascular support.

The purpose of this dissertation is to re-evaluate a tried and tested technique, and possibly prevent it from being abandoned for the wrong reasons.

1.2 HYPOTENSION AND SPINAL ANAESTHESIA - Maternal and foetal effects

The most important physiological effect of spinal anaesthesia is hypotension. The decrease in arterial pressure is more severe and occurs more rapidly in the pregnant patient than in the non-pregnant patient [3]. This relates to the so called 'supine hypotension syndrome' of pregnancy caused by compression by the gravid uterus of the inferior vena cava, pelvic veins and the aorta. This 'potential' syndrome is prevented by a reflex increase in neurogenic vasoconstrictor tone. Spinal anaesthesia abolishes this compensatory mechanism.

Spinal hypotension results more from dilatation of veins than of arteries [14]. When local anaesthetic agents are injected into the subarachnoid space a preganglionic sympathetic denervation occurs. Unlike denervated arteries, denervated veins dilate maximally causing gravity dependent peripheral venous pooling. As a result cardiac preload decreases, cardiac output decreases and consequently blood pressure decreases [3].

The incidence of hypotension in spinal anaesthesia is less in labouring (approximately 50%) than in non-labouring patients (approximately 92%) [15]. This may be as a result of the autotransfusion of the vascular system with approximately 300ml of blood with each uterine contraction. It may also relate to the fact that labouring patients are receiving intravenous fluid therapy and often oxytocic agents (syntocinon, used to increase uterine contraction) whereas non-labouring patients are relatively dehydrated by pre-operative starvation.

The degree of sympathetic block tends to be greater, and the onset of hypotension faster, after spinal than after epidural anaesthesia [16]. This is because the speed of onset of the block is faster than the development of any physiological compensation.

The major factor in the development of hypotension is the level of the block [17]. Sympathetic outflow is between T1 and L2. Fibres from T2 to T4 provide the sympathetic supply to the heart and decreased contractility and bradycardia (from unopposed vagal activity) ensues if they are blocked [17]. A block as high as T1 may completely remove the ability of the body to compensate for other circulatory changes and in addition produces extensive vaso- and veno-dilatation. Individual variations in technique such as speed of injection or the use of barbotage may cause different degrees of hypotension by altering the height of block obtained and the rate at which it develops.

The minimum acceptable blood pressure with regard to maternal and foetal well being remains speculative [14]. When mean arterial pressure falls below 50mmHg, decreases in cerebral blood flow may result in depressed consciousness, depressed respiration and nausea and vomiting. An editorial in the Lancet in 1989 suggested that the rapidity with which the pressure falls and the symptoms that are produced are probably as important as the actual measurement [18].

Cardiac arrest during sub-arachnoid anaesthesia is an uncommon, but well reported phenomenon [13]. It may relate, in high blocks, to profound bradycardia caused by unopposed parasympthetic input. Alternatively, it may be due to decreased venous return, which may trigger reflexes mediated by caval and atrial receptors, or result from electromechanical dissociation.

Maternal hypotension has been well shown to have a deleterious effect on the foetus. The uterus autoregulates inefficiently and any decrease in its perfusion pressure results in reduced uteroplacental and intervillous blood flow [3]. This alters the exchange of oxygen, carbon dioxide and nutrients with the foetus. Marx et al., in 1969, showed that maternal hypotension causes foetal acidosis [19]. These findings have been confirmed by subsequent animal and human trials [10,11,20,21].

A study in 1978 showed significant correlation between maternal hypotension (of 4 - 8 minutes duration) and weak rooting and sucking reflexes in infants up to 4 - 7 days post-delivery [22]. In contrast, a subsequent study in 1982, using the Scanlon early neonatal neurobehavioural scale showed that a short period of hypotension (less than 2

minutes), did not alter neurobehavioural performance despite causing altered neonatal acid-base values [23]. It is apparent that maternal hypotension only endangers the foetus when there is pre-existing foetal compromise or when hypotension is particularly profound or prolonged.

The aggressive prevention of hypotension is prudent, particularly when high spinal blockade is deliberately achieved. Hypotension due to spinal anaesthesia causes considerable maternal discomfort, nausea and vomiting. Initial mild hypotension may progress rapidly to cardiovascular and respiratory collapse. In addition, maternal hypotension may cause transient foetal asphyxia.

1.3 EPHEDRINE AND SPINAL ANAESTHESIA - Maternal and foetal effects

Ephedrine is a non-catecholamine sympathomimetic alkaloid [24]. It is the active principle of the plant MaHuang and has been used for centuries in China. Ephedrine stimulates both $alpha_1$ and $beta_1$ receptors (having vascular and cardiac effects respectively) and acts both directly and indirectly. It may be used intramuscularly as local vasoconstriction is insufficient to delay systemic absorption.

Ephedrine is resistant to metabolism by monoamine oxidase (MAO) in the gastrointestinal tract so that unchanged drug is absorbed into the circulation following oral administration [25]. It is also resistant to metabolism by catechol-o-methyl-transferase (COMT) thus permitting a relatively long duration of action. Up to 40% of a single dose of ephedrine is excreted unchanged in the urine [25]. Some ephedrine is deaminated by MAO in the liver where conjugation also occurs [25]. This slow inactivation and excretion of ephedrine are responsible for its prolonged duration of action. Ephedrine is associated with tachyphylaxis i.e. a second dose produces a less intense blood pressure response than the first dose. Tachyphylaxis may relate to a persistent blockade of adrenergic receptors by ephedrine or may be due to depletion of noradrenaline stores [25].

Ephedrine has been found to have an anti-emetic effect of its own, without the sedative

side effects of other anti-emetics. Central nervous system stimulation does occur but to a lesser extent than that with other similar drugs such as amphetamines [25].

The role of ephedrine in anaesthesia is in cardiovascular support, particularly after local anaesthetic induced sympathetic blockade. This blockade causes venous pooling, decreased peripheral resistance, decreased cardiac output, occasionally decreased myocardial contractility and decreased heart rate. Ephedrine acts almost as a physiologic antagonist to each of these depressant actions.

The cardiovascular effects of ephedrine resemble adrenaline, but its blood pressure elevating action is less intense and lasts substantially longer. These effects are due in part, to alpha receptor mediated peripheral arterial and venous constriction. The principle mechanism, however, for cardiovascular effect is increased myocardial contractility as a result of activation of beta-1 receptors. A study in 1986 demonstrated the efficacy of ephedrine in correcting both the venous capacitance and the arterial resistance after spinal anaesthesia in a cardiopulmonary bypass-canine model [26]. In contrast, a study in 1995, found that a low dose infusion of ephedrine caused relatively little arterial or venous constriction but increased systolic arterial pressure by increases in stroke index and heart rate [27]. The more profound vasoconstrictor effect seen in the former study may be accounted for by the higher doses of ephedrine used i.e. vasoconstriction is dose related.

Whether or not ephedrine has a deleterious effect on uteroplacental blood flow and consequently on the foetus has been a question of some contention. Several animal studies have convincingly demonstrated the safety of ephedrine [20,21,28]. However, human clinical studies have been somewhat contradictory in their findings, particularly where ephedrine has been used intramuscularly. Studies by Ward et al., and Gutsche, in epidural and spinal anaesthesia respectively, did not demonstrate any adverse effect of intramuscular ephedrine on foetal gas exchange [9,29]. In contrast, studies by Rolbin et al. and Rout et al. both detected adverse changes in umbilical cord acid-base status when intramuscular ephedrine was given in epidural and general anaesthesia respectively [1,2]. No study has shown reduced Apgar or neurobehavioral scores associated with ephedrine administration.

Two studies have demonstrated foetal and neonatal tachycardia associated with ephedrine administration [29,30]. However, both agree that there was no evidence that these effects on foetal heart rate were due to asphyxia. It is likely that these effects were due to the direct action of ephedrine which has been shown to cross the placenta extensively.

Ephedrine remains widely accepted as the vasopressor of choice for treating maternal hypotension associated with neuraxial anaesthesia.

1.4 LITERATURE REVIEW

1.4.1 Vasopressors - the early years.

In 1927 a study by Ockerblad and Dillon introduced the method of using ephedrine to prevent hypotension in spinal anaesthesia for urological procedures [4]. They used ephedrine 100mg subcutaneously before systolic pressure dropped below 100mmHg and although they did note an increase in pulse rates, described the technique as "of immense practical use in spinal anaesthesia".

Casady and Moore in 1960 cautioned against the use of prophylactic vasoconstrictors in regional anaesthesia for vaginal delivery [6]. This was based on a prospective study of 747 patients who received prophylactic intramuscular methoxamine before continuous caudal anaesthesia for vaginal delivery. The patients had also received the oxytocic agent ergonovine maleate at the time of placental delivery. It was postulated that the combination of vasoconstrictors and oxytocics was associated with severe post operative hypertension. Systolic blood pressures of greater than 140mmHg developed in 4,6% of their patients. The study was terminated when a patient with hypertension suffered a ruptured cerebral aneurysm. This event may have resulted in a decline in the use of prophylactic administration of vasoconstrictors (the study had been prompted by a report of a ruptured intracranial aneurysm 2 hours post delivery in 1957). It should be noted that ephedrine was not used in this study and the oxytocics used were ergot derivatives with known vasoconstrictor effects.

In 1962 a retrospective study by Moya and Smith examined the changes in blood pressure and pulse rate related to vasopressors, dose of local anaesthetic, level of anaesthesia and use of oxytocic drugs [5]. They studied the charts of 1633 Caesarean sectioned patients over the period 1952 to 1960. They found that 82% of patients had received prophylactic vasopressors, 72% of them 50mg of intramuscular ephedrine. In spite of this, in 54% of the cases systolic blood pressure had dropped below 100mmHg. This may relate to the fact that 5% dextrose water, which is an ineffective volume expander, was used as a fluid preload. They also assessed the incidence of reactive hypertension when combining ephedrine with different oxytocics. When ephedrine was used with oxytocin, only 1,5% of patients developed an elevation in blood pressure of greater than 40mmHg. When ephedrine was used with ergonamine, 5,7% of patients developed this degree of hypertension.

In 1965, Greiss and Crandell et al., using a pregnant sheep model, showed that simulated hypotension was associated with reduced uterine blood flow [31]. They showed that certain vasopressor drugs, namely levarterenol, phenylephrine and angiotensin did not improve uterine blood flow despite restoring maternal blood pressure. They showed that rapid infusions of 5% dextrose or dextran solutions significantly improved both mean blood pressure and uterine blood flow. They suggested that prophylactic or therapeutic use of vasopressor agents in pregnancy be contraindicated and recommended therapy designed to increase circulating blood volume.

1.4.2 The changing role of fluid preloading.

Wollman and Marx demonstrated the value of fluid pre-loading in spinal anaesthesia in 1968 [7]. In a small study of 14 patients for Caesarean section or vaginal delivery, pre-treatment with 1000ml of 5% glucose in Ringer's lactate solution prevented any significant decrease in arterial pressure, whereas the control group all became hypotensive. This study is widely quoted and until recently, fluid pre-loading has been accepted as a satisfactory method of preventing hypotension. It should be noted that 43% of their study group patients were in active labour and therefore significantly less prone to hypotension. These findings were supported when the following year the same

group, publishing under Marx, compared the prevention of hypotension to the treatment of hypotension with regard to foetal outcome [19]. Significant foetal acidosis (pH 7,18) and relatively low Apgar scores were associated with hypotension. They showed better foetal biochemical condition and healthier neonates when hypotension was prevented than when it was treated. As in their previous study, they emphasised intravenous hydration as a preventative measure but did find that a small dose (12,5mg) of intravenous ephedrine was a useful adjunct.

Subsequent studies have confirmed Marx's findings with regard to the effect of hypotension on the foetus but have not supported her findings with respect to the efficacy of fluid preloading.

In 1976 Clark et al. studied the effects of fluid loading and left uterine displacement in the prevention of hypotension [15]. They achieved left uterine displacement with a 'sluder' (sustained left uterine displacer).They showed an incidence of hypotension of 92% when no preventive measures were taken in patients for elective Caesarean section. With fluid loading and left lateral tilt combined, the incidence was reduced to 53%, and with fluid loading alone, to 57%. Thus although these conservative methods reduced the incidence of hypotension, the incidence remained unacceptably high. Clarks' findings conflicted with those of Wollman et al., who showed no significant change in mean arterial pressure after a preload of one litre of Ringer's lactate solution. Clark et al. comment that Wollman et al's use of mean pressure in their study may have obscured the fact that systolic pressure could fall below 100mmHg. It was also notable in this study that patients in labour had significantly lower incidences of hypotension (50%) than patients out of labour (92%). This was reduced to 14,7% with fluid preloading and uterine displacement. This finding suggests that prophylactic ephedrine may only be necessary in patients for elective Caesarean section.

In 1993 Rout et al. published a study that re-evaluated the efficacy of fluid preloading in spinal anaesthesia [32]. They compared the haemodynamic effects of using a 20ml per kg intravenous preload to using no preload in 140 patients for elective Caesarean section. They noted that there was a 16% (from 71% to 55%) reduction in

the incidence of hypotension in the preload group. This difference, although statistically significant, was adjudged to be clinically insignificant.

In 1995, Jackson et al. performed a similar study on 60 women for elective Caesarean section, but used ephedrine on a prophylactic basis as an infusion [33]. They compared the protective effect of a 1000ml fluid preload with that of a 200ml fluid preload. Both were administered 10 minutes before spinal anaesthesia was induced. They found that there was no significant difference in ephedrine requirements between the 2 groups, or in the incidence, severity or duration of hypotension. They advocated abandoning routine fluid preloading before regional anaesthesia.

1.4.3 Ephedrine - vasopressor of choice in pregnancy.

Schnider et al. published an animal study in 1968, which convincingly demonstrated the efficacy of ephedrine in treating hypotension [20]. Using a pregnant ewe model, they monitored maternal and foetal blood pressures and arterial gases through a period of spinal hypotension and then through a recovery period initiated by ephedrine. They showed that when ephedrine was used to correct spinal hypotension, the foetal deterioration that had occurred was arrested and there was an improvement in foetal oxygenation, carbon dioxide elimination and fixed acid excretion.

In 1970, James et al. published another animal study in response to the studies by Greiss and by Schnider, whose findings on vasopressors in pregnant ewes conflicted [21]. James et al. compared the effects on uterine blood flow of 3 different vasopressors: ephedrine, metaraminol and mephenteramine. As in previous studies, they used a pregnant ewe model. They found that ephedrine and mephenteramine did significantly increase uterine blood flow but never to more than 90% of pre spinal levels. They noted that higher doses caused increasing alpha-receptor stimulation and concluded that these vasopressors should be reserved for circumstances where other measures have failed.

In 1971, while comparing the effects of methoxamine and ephedrine in normotensive pregnant primates, Eng et al. unexpectedly found a significant decline in uterine blood

flow after an intravenous ephedrine infusion was discontinued [34]. The study confirmed that methoxamine caused relative foetal asphyxia by reducing uterine blood flow. They showed that ephedrine was relatively innocuous but expressed concern about potential foetal danger after discontinuation of the infusion.

Ralston et al. in 1974, attempted to provide a correlation between maternal blood pressure responses to various drugs and simultaneous changes in uterine blood flow and foetal acid-base status [28]. They administered ephedrine, metaraminol, mephenteramine and methoxamine to 16 non-anaesthetised pregnant ewes. When maternal blood pressure was increased by 50%, uterine blood flow was unchanged with ephedrine and was reduced 20% with mephentermine, 45% with metaraminol and 62% with methoxamine. No significant change in foetal blood gas and acid-base variables was demonstrated. In their discussion they comment on the difference between their results and those of Eng et al. who had found ephedrine to be potentially harmful. It is their belief that the reduced uterine blood flow found by Eng after ephedrine infusion may have been due to a deterioration in their experimental animal preparation. They conclude that ephedrine is the vasopressor of choice in pregnancy.

1.4.4 Methods of ephedrine administration.

1.4.4.1 Intramuscular.

In 1976 Gutsche attempted to combine intramuscular ephedrine (that had been found to be relatively ineffective by Moya et al.), with fluid preloading and uterine displacement (that was found to be relatively ineffective by Clark et al.) [9]. He performed a controlled study on 17 patients undergoing elective repeat Caesarean section under high subarachnoid block (T5-T1 sensory level). By using 50mg of ephedrine intramuscularly before induction, combined with an intravenous preload of 500mls of Ringer's lactate solution and left lateral tilt, he was able to reduce the incidence of hypotension from 100% in his control group to 25%. He showed no reactive hypertension and detected no evidence of foetal gas exchange abnormalities. The study could be faulted for its use of a pharmacologically active

drug, procaine, as its placebo and for its small sample size. To the candidate's knowledge, this study has not been repeated on a larger scale.

In 1979, Ward et al. used intramuscular ephedrine prior to epidural anaesthesia in an attempt to document the placental transfer of the drug, and to report on the foetal and neonatal effects of this transfer [29]. They administered 25 or 50mg of ephedrine intramuscularly together with a fluid preload and left uterine displacement. Maternal cardiovascular status was found to be stable during the anaesthetic. In spite of finding foetal blood ephedrine levels to be approximately equal to maternal levels, they detected no measurable deleterious effects on foetal wellbeing or neonatal outcome.

Rolbin et al. evaluated the use of intramuscular ephedrine in elective Caesarean sections under epidural anaesthesia [1]. They demonstrated an unacceptably high incidence of reactive hypertension (in their 50mg ephedrine group 75% of patients developed blood pressures greater than 20% above baseline and 50% developed blood pressures greater than 30% of baseline). They showed a lack of efficacy in preventing hypotension in a 25 and a 50mg group (incidences of hypotension in the control, 25 and 50mg groups were 12%,12% and 14% respectively). As a result of the detection of acid base abnormalities in arterial cord blood of the 50mg group, the study was terminated prematurely. No significantly low Apgar or neurobehavioural scores were detected. It should be noted that findings in epidural anaesthesia are not necessarily relevant to spinal anaesthesia - the physiologic changes, although essentially the same, differ markedly in their timing and severity.

Brizgys et al., in 1987, performed the first large scale prospective study on the incidence of epidural hypotension since that of Casady in 1960 [35]. They studied 583 labouring and non-labouring women undergoing repeat and primary Caesarean section under epidural anaesthesia. They determined the incidence of maternal hypotension and its effects on neonatal clinical and acid-base status. Their results indicated an overall incidence of maternal hypotension in epidural anaesthesia of 29%. In the early stages of the study intramuscular ephedrine (25 or 50mg) was used but was discontinued when clinical observation showed no clear

prophylactic benefit. Some benefit of intramuscular ephedrine was evident in non-labouring mothers where the incidence of hypotension was reduced from 41% to 33%. Although findings in this study apply only to epidural anaesthesia, they do support the theory that prophylactic intramuscular ephedrine has a greater role in non-labouring mothers than in labouring mothers.

The only controlled study in the English literature in which 37,5mg of ephedrine was used intramuscularly to prevent spinal hypotension was performed in 1989 in a non-obstetric population (lower limb and lower abdominal procedures) by Hemingson et al [36]. The study group was given 37,5mg of intramuscular ephedrine combined with an intravenous bolus of 12,5mg. Haemodynamic responses of this group were compared to those of a placebo group. They showed that in ASA III patients, there was a marked reduction in mean arterial pressure in the placebo group (30,8mmHg) which differed significantly from that in the ephedrine group (5,2mmHg). All ASA III patients in the placebo group had a reduction of mean arterial pressure of more than 20%. They concluded that it is appropriate to administer ephedrine in this manner prior to spinal anaesthesia particularly to patients of ASA class III.

In 1992 Rout et al. designed a study to illustrate a specific concern that they had with prophylactic intramuscular ephedrine [2]. The concern was the eventuality of giving intramuscular ephedrine and then failing to perform a spinal anaesthetic (the incidence of spinal failure being of the order of 4%). They argued that if general anaesthesia was resorted to subsequently, the combination of vasopressor and general anaesthesia would result in deleterious effects to both the mother and the foetus.

They studied 30 parturients for elective Caesarean section under general anaesthesia. They compared the haemodynamic effects on the mother, and biochemical and clinical effects on the foetus; of a placebo, 25mg and 50mg of ephedrine intramuscularly. Their results showed that 50% of the 50mg group developed blood pressures of greater than 30% of control. They noted that neonatal acid-base status was impaired in the 50mg group as evidenced by an

umbilical arterial pH of 7,16. In their view, the potential foetal risk in the event of a failed spinal was not justified by the cardiovascular responses; which they found to be inadequate in 50% of patients receiving 25mg, and excessive in 50% of patients receiving 50mg of ephedrine. On the basis of this conclusion, they state that *the prophylactic administration of intramuscular ephedrine prior to spinal anaesthesia for Caesarean section is not to be recommended.*

The above statement forms the basis for the dissertation by this candidate.

1.4.4.2 Intravenous.

Kang et al. introduced the concept of using an intravenous infusion of ephedrine on a prophylactic basis in spinal anaesthesia [10]. They titrated an infusion of 0,01% ephedrine to maintain systolic blood pressure at 90-100% of baseline in 20 patients. By doing this they were able to reduce the incidence of hypotension to 10% (the lowest documented incidence in the literature). They noted a significantly higher incidence of nausea and vomiting in their control group who were treated with intravenous boluses of ephedrine when systolic blood pressure fell below 80% of baseline. They also noted in their control group that blood pressure did not return to baseline levels until approximately 6 minutes after 'rescue' therapy was started.

In a similar theme and in the same year, Datta et al. demonstrated the virtue of giving intravenous boluses of ephedrine earlier than had been previously recommended [11]. A bolus of 10-30mg was given as soon as any fall from baseline blood pressure was detected. Combining this method with a large fluid preload (1500mls of Ringer's lactate solution), they reduced the incidence and severity of hypotension significantly. As in the above study, they showed a marked reduction in the incidence of nausea and vomiting in their study group. This reinforces the belief that nausea and vomiting are related to hypotension with consequent hypoxaemia of the medullary vomiting centres. Datta et al. also showed significantly better foetal acid-base status in subjects where systolic blood

pressure remained above 100mmHg compared to those where blood pressure dropped below 100mmHg.

In 1984 Hollmen et al. used radioactive xenon to measure intervillous blood flow before and after epidural anaesthesia [37]. They studied 18 patients, 9 of whom received a prophylactic intravenous bolus of 15mg ephedrine and 9 of whom did not. They were able to show that an intravenous bolus of ephedrine did not significantly alter intervillous blood flow. Of interest was the finding that in 88% of patients who had received the intravenous bolus, blood pressures had decreased to below pre-block and pre-ephedrine levels 20-25 min later. Based on this finding, they suggested that an intravenous infusion would be preferable to an intravenous bolus of ephedrine. In the candidate's opinion, the intramuscular route may also be of advantage in this regard.

In the same year, the same group of investigators, publishing under the name Jouppila, used the same radioactive xenon techniques to measure intervillous blood flow, this time under spinal anaesthesia [38]. They demonstrated, in 9 subjects, that the use of a preload of 1500 to 2000mls of Ringer's lactate solution with the early administration of an ephedrine infusion can prevent a reduction in placental blood flow despite a moderate decrease in maternal blood pressure.

1.4.5 Editorials and review articles.

In 1989 an editorial on circulatory changes after epidural block for Caesarean section appeared in the Lancet [18]. The editorial concluded that since vasodilation is the common factor in all cases, the judicious use of vasopressors is the most effective and rapid way to reverse hypotension. It is observed that ephedrine is not only rapidly effective in restoring blood pressure but that it quickly reverses symptoms of vagal overactivity such as nausea and vomiting. Intravenous fluids are described as unreliable as a prophylactic measure and too slow to be of use in treatment.

McCrae and Wildsmith reviewed the prevention and treatment of hypotension during central neural blockade in the British Journal of Anaesthesia in 1993 [17]. Summarising the literature on fluid preloading they state that studies are contradictory even in the incidence of hypotension in the control groups. They comment that infusions of large volumes of fluid have been shown to overload the right side of the heart and that obstetrical patients are at increased risk for pulmonary oedema because interstitial lung water is increased during the puerperium. They suggest that a more physiological approach to the treatment of hypotension induced by sympathetic block is to counteract it as it occurs by using sympathomimetic drugs. As regards intramuscular ephedrine, McCrae and Wildsmith were influenced largely by Rolbin's study that was done in epidural anaesthesia. They describe the modality as not reliably preventing hypotension and being associated with unacceptable hypertension. They recommend awaiting the onset of hypotension and then treating it with intravenous ephedrine.

In 1995, Morgan reviewed spinal anaesthesia in obstetrics in the Canadian Journal of Anaesthesia [3]. She took cognisance of Rout's finding that preloading did not eliminate the hypotension associated with spinal anaesthesia. However, she quotes a letter by Bassell and Marx that points out the salutary effect of volume on uteroplacental blood flow and cautions against not preloading patients [39]. Morgan was also guided by the Rolbin study in her approach to intramuscular ephedrine and also advocated awaiting the onset of hypotension and then treating it immediately with fluid and vasopressors.

1.4.6 Summary.

For the sake of clarity the general trends in the literature are summarised as follows:

- Spinal anaesthesia in obstetrics becomes popular in the 1940's
- In the 1950's, prophylactic intramuscular vasopressors are widely used in managing hypotension
- In the 1960's prophylactic vasopressors are brought into disrepute by reports of hypertensive complications and concerns about the effect of vasopressors on uteroplacental blood flow

- In the 1960's and early 1970's animal trials show conclusively that direct acting alpha stimulants do reduce uteroplacental blood flow. Ephedrine is found to be safe.
- Fluid preloading becomes the mainstay of hypotension prophylaxis after studies in the late 1960's demonstrate the efficacy thereof.
- In 1976, a small controlled study by Gutsche in spinal anaesthesia found prophylactic intramuscular ephedrine to be safe and to reduce the incidence of hypotension to 25%.
- During the 1970's and 1980's epidural anaesthesia is favoured over spinal anaesthesia for Caesarean section.
- In 1982, intramuscular ephedrine is evaluated in epidural anaesthesia where it is found to be ineffective and to cause hypertension and foetal acidosis.
- In the 1990's spinal anaesthesia enjoys a resurgence in popularity.
- In the 1990's, 2 studies demonstrate the inadequate protective effect of fluid preloading.
- In 1996, vasopressors, particularly ephedrine, continue to play an important role in the management of spinal hypotension but the manner in which they are used remains contentious.

It is the candidate's impression that the apparent lack of consistency of results in the literature may be due to inadequate standardisation. Studies are compared which differ in type of anaesthesia (spinal or epidural), type of patient (differing size; labouring or non-labouring), and height of block. It may be useful therefore, to reproduce and validate previous research. This study will repeat research done by Gutsche in 1976 but will differ in using a larger sample size, a more appropriate placebo and a lower dose of ephedrine [9].

1.5 AIMS OF THE STUDY

1.5.1 Statement of the Problem.

There are various aspects regarding the use of prophylactic intramuscular ephedrine that require clarification.

- Is a bolus dose of 37,5mg of intramuscular ephedrine potentially harmful:
  - to the mother by causing hypertension and tachycardia?
  - to the foetus by compromising placental gas exchange?

- Is a bolus dose of 37,5mg of intramuscular ephedrine effective in preventing hypotension caused by spinal anaesthesia?

1.5.2 Null Hypotheses.

- An intramuscular bolus of 37,5mg of ephedrine causes no significant maternal hypertension and tachycardia.
- An intramuscular bolus of 37,5mg of ephedrine causes no significant foetal acidosis.
- An intramuscular bolus of 37,5mg of ephedrine does not reduce the incidence or severity of hypotension following spinal anaesthesia.

CHAPTER 2

MATERIALS AND METHODS

2.1 STUDY POPULATION AND PATIENT SELECTION.

Forty (40) patients of ASA physical status I and II, presenting for elective Caesarean section at Baragwanath Hospital, were entered into the study. Institutional ethical committee approval was obtained and all the patients gave informed consent (appendix B). The study was also approved by the Pharmaceutics and Therapeutics committee of Baragwanath Hospital. All patients were given the choice of withdrawing from the study at any time (appendix B). All consenting patients were entered into the study. Exclusion criteria included the following-

- obesity which resulted in an inability to palpate lumbar spines
- hypertension (blood pressure greater than 150/90)
- conventional contraindications to spinal anaesthesia i.e.coagulopathy, sepsis, lack of consent, hypovolaemia (clinically assessed).

The patients were admitted to the hospital at least one day prior to surgery. The candidate performed a pre-operative assessment on all the patients on the morning of surgery, and at this point asked the patients whether they would consent to enter the study. The patients were presented with an information sheet (appendix A) and a consent form (appendix B) and were asked to peruse them. Written consent was then obtained from those who agreed to enter the study.

All of the patients entered into the study were randomly allocated to one of two groups. Randomisation was achieved by placing slips of paper labelled as follows in sealed envelopes:-

- Ephedrine
- Normal saline

Twenty (20) of each of these slips of paper were placed in unmarked individual envelopes resulting in a total of forty (40) envelopes. The envelopes were shuffled into random order and placed in a box. As each patient arrived in the operating theatre an

assistant opened an envelope which indicated to him which syringe, either ephedrine or normal saline, he should prepare for the candidate. The candidate was unaware of which of the two solutions he would administer as an intramuscular injection.

Spinal anaesthesia would then be administered in the manner described below (see Method 2.3).

2.2 MATERIALS.

2.2.1 Monitoring equipment

- A Criticon dinamap (Johnson and Johnson, South Africa) was used to measure systolic, diastolic, mean blood pressure and pulse rate non invasively.
- An ECG machine provided continuous ECG monitoring (Diascope 2, S & W Medico Teknik A/S, Denmark).
- A pulse oximeter (Ohmeda, Louisville U.S.A.) monitored oxygen saturation continuously.

2.2.2 Subarachnoid injection

- 25 G Spinocan Quinke needles for administering the spinal anaesthetic.
- local anaesthetic solution was constituted as follows:
  - 4,5mls bupivacaine 0,5% was admixed with 0,5ml of 50% dextrose water to achieve 5mls of 0,45% hyperbaric bupivacaine.
  - 2,5mls (11,25mg bupivacaine) of this solution was injected into the subarachnoid space.

2.2.3 Umbilical cord blood sampling

- 2ml heparinised syringe
- Ilex blood gas analyser IL 1640 (Milano, Italy)

2.2.4 Other intravenous medications

- syntocinon 20 units
- cefoxitin 1gm

2.3 METHODS

All patients were starved and prepared as for Caesarean section under general anaesthesia. They were premedicated with an oral dose of 30mls of 0,3 molar sodium citrate.

On entering the operating theatre the patient was placed in the recovery room area, an intravenous cannula (18 G) placed in a left forearm vein and the monitoring equipment described above attached. The cuff of the dinamap was placed around the right arm and blood pressure and heart rate monitored at 3 minute intervals to obtain baseline readings. The mean of three values was used provided that the systolic pressure did not vary by more than 10%. Following baseline readings, patients received an intravenous infusion of 500mls of Ringer's lactate solution over a period of approximately 15 minutes.

Patients were then moved into the theatre and placed on the operating table in a conventional sitting position. At this point patients received an intramuscular injection into the left deltoid of either normal saline or ephedrine. Following this injection the values of the blood pressure and the pulse rate were manually recorded at one minute intervals for a period of 30 minutes and thereafter at 5 minute intervals for 40 minutes and then at 10 minute intervals for 20 minutes (appendix C).

After local infiltration of the skin with 2mls of 2% lignocaine, spinal anaesthesia was administered by the candidate under aseptic conditions - 2,5mls of 0,45% hypertonic bupivacaine was injected through a 25 G Quinke needle inserted at the L3 L4 interspace.

After injection of the anaesthetic solution, the patient was placed in a supine position and tilted 15 degrees to the left. Oxygen at 8 litres per minute was administered via a plastic disposable face mask from the time of induction of anaesthesia until termination of surgery. The spread of the sensory blockade was tested with an ice cube 15 minutes after subarachnoid injection.

If maternal hypotension (defined as a fall in systolic blood pressure of more than 30% or to below 100mmHg) occurred, ephedrine was given intravenously, 5mg doses every minute, until the systolic arterial pressure rose to at least 100mmHg. The rate of intravenous fluid infusion was also increased over that period.

The blood loss and total volume of intravenous fluid administered were assessed and recorded by the assistant. In addition to the physiological parameters recorded, any complications during the procedure were noted. Such complications included nausea, vomiting and pain.

Times of ephedrine injection, spinal injection, skin incision, uterine incision, delivery of the baby and conclusion of surgery were recorded by an assistant. The time from uterine incision to umbilical cord cross clamp was recorded by the candidate with a stop watch (appendix D).

The foetus was assessed by Apgar scoring at 1 and 5 minute intervals by the assistant. At delivery, a sample of umbilical venous blood from a doubly clamped segment of umbilical cord was collected. Blood gases were immediately determined with an Ilex blood gas analyser (appendix E).

At the conclusion of surgery, patients were transferred to the recovery room for continued monitoring and recording of haemodynamic parameters. If maternal hypotension occurred, intravenous ephedrine boluses were given in the same manner as above.

Ninety (90) minutes after the intramuscular injection, monitoring was discontinued and the patient discharged to the ward.

Data was recorded manually on the data sheets (appendix C).

2.4 STATISTICAL ANALYSIS

The following statistical tests were performed as appropriate using the GraphPad Instat programme, version 2,05A (GraphPad Software Inc., San Diego, California, USA)

2.4.1 Fisher's Exact Probability Test

2.4.2 Student's t-test for unpaired samples

Any P value of less than 0,05 was considered statistically significant. The results and the statistical tests performed to analyse the results are discussed in Chapter 3.

CHAPTER 3

RESULTS

As discussed in Chapter 2, twenty patients in the study group received an intramuscular injection of 37,5mg of ephedrine and twenty patients in the control group received an intramuscular injection of normal saline prior to spinal anaesthesia.

3.1 DEMOGRAPHIC DATA

Table 3.1

The mean values for age, weight, height and delivery time and the mode value for level of sensory block for the two groups. Delivery time was defined as the time interval from uterine incision to clamping of the umbilical cord.

	AGE- years	WEIGHT- kg	HEIGHT- cm	DELIVERY TIME- seconds	HEIGHT OF SENSORY BLOCK
CONTROL GROUP	30 (sd 5,5)	77 (sd 14,3)	161 (sd 6,2)	92 (sd 30)	T2
STUDY GROUP	28 (sd 4,5)	82 (sd 13,3)	164 (sd 4,7)	86 (sd 31)	T2
t	1.26	1.14	1.72	0.62	
P	0.21	0.26	0.09	0.53	

The two groups (Table 3.1) were compared in respect of age, weight, height and delivery time by means of the Student's t-test. No statistically significant differences were found between the groups.

The ASA physical status of the two groups was as follows-

- Control group: 18 subject ASA I and 2 subjects ASA II
- Study group: 20 subjects ASA I

The mean baseline systolic blood pressures for the two groups were as follows-

- Control group: 125 (sd 12,4)
- Study group: 123 (sd 13,2)

3.2 HYPERTENSION - THE INCIDENCE AND SEVERITY.

Table 3.2

The number of patients in each group in whom reactive hypertension occurred. Reactive hypertension was defined as an increase in systolic blood pressure of more than 30% from baseline after ephedrine was administered.

	CONTROL GROUP	STUDY GROUP
Hypertension	4	6
No hypertension	16	14

The prevalence of hypertension was compared between the two groups by means of Fisher's Exact Probability Test. *No statistically significant difference was found.* The P value was 0,716.

Table 3.3

The number of patients in each group in whom persistent hypertension occurred. Persistent hypertension was defined as an increase in systolic blood pressure of greater than 30% from baseline occurring in the post-operative period.

	CONTROL GROUP	STUDY GROUP
Persistent hypertension	0	1
No persistent hypertension	20	19

The two groups were compared in respect of persistent hypertension by means of Fisher's Exact Probability Test. *No statistically significant difference was found.* The P value was 1,0.

Table 3.4

The raw data and mean values for the highest recorded blood pressures occurring in patients from the two groups.

	CONTROL GROUP	STUDY GROUP
1	166	150
2	161	176
3	155	141
4	150	139
5	171	156
6	133	158
7	142	160
8	156	150
9	166	148
10	127	136
11	139	175
12	136	148
13	147	161
14	162	157
15	146	157
16	142	149
17	147	137
18	150	143
19	160	152
20	141	163
Mean	150	153
Standard deviation	12	11, 2

The raw data, mean and standard deviation are listed in Table 3.4 above and shown as a bar chart for emphasis in Figure 3.1.

The two groups were compared in respect of the above by means of the Student's t-test. *No statistically significant difference was found.*

The P value was 0,4188 (t value of 0,82).

FIGURE 3.1

A bar chart of the mean values of the highest systolic blood pressures for the two groups.

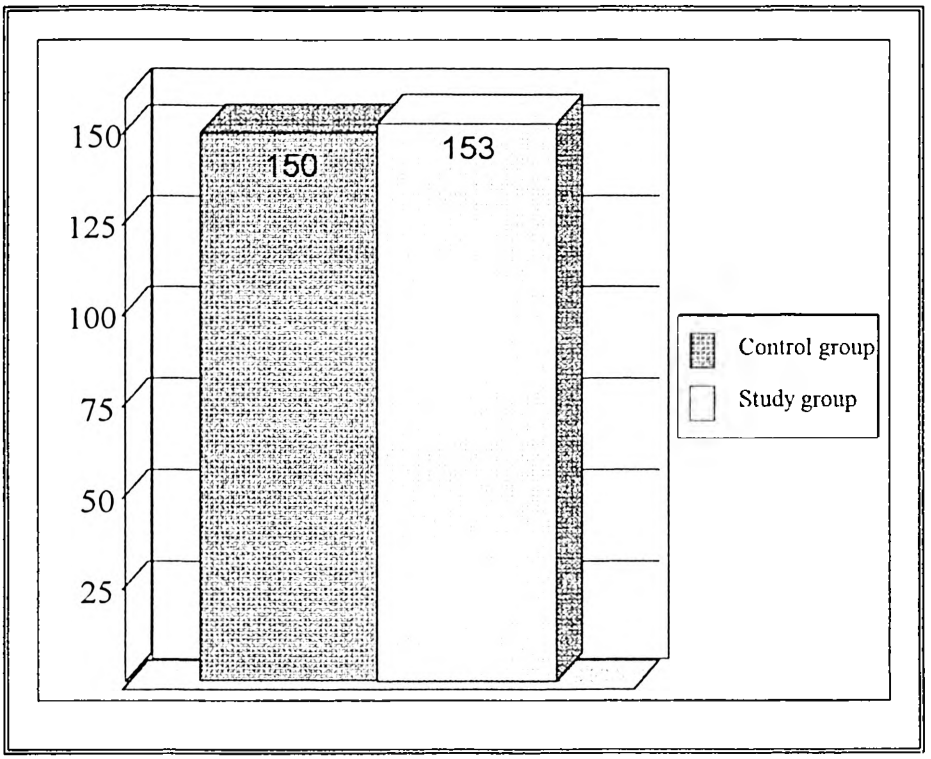


Table 3.5

The mean systolic blood pressures of both groups immediately before subarachnoid injection and immediately following delivery.

	Blood pressure pre-spinal injection	**Blood pressure** post-delivery
CONTROL GROUP	133mmHg (sd 14,9)	122mmHg (sd 14,6)
STUDY GROUP	140mmHg (sd 9,8)	127mmHg (sd 11,6)

The two groups were compared in respect of the above by means of the Student's t-test. *No statistically significant differences were found.* The P values were as follows -

- blood pressure pre-spinal injection P=0,087 (t value of 1,76)
- blood pressure post-delivery P=0,277 (t value of 1,20).

3.3 TACHYCARDIA - INCIDENCE AND SEVERITY

Table 3.6

The number of patients in each group in whom tachycardia occurred. Tachycardia was defined as a heart rate of greater than 120 beats per minute.

	CONTROL GROUP	STUDY GROUP
Tachycardia	13	14
No tachycardia	7	6

The two groups were compared in respect of the prevalence of tachycardia by means of Fisher's Exact Probability Test. *No statistically significant difference was found.*
The P value was 1,00.

Table 3.7

The means of all heart rates recorded in the first 30 minutes and the means of the highest heart rates recorded.

	Mean pulse rate - first 30 minutes	**Mean highest pulse rate**
CONTROL GROUP	92 beats per minute (sd 13,8)	123 beats per minute (sd 20,5)
STUDY GROUP	96 beats per minute (sd 16,6)	130 beats per minute (sd 21,4)

The two groups were compared in respect of the above by means of the Student's t-test. *No statistically significant differences were found.* The P values were as follows-

- mean pulse rate P=0,413 (t value of 0,83)
- mean of highest pulse rates P=0,293 (t value of 1,07).

3.4 HYPOTENSION - INCIDENCE AND SEVERITY.

In the analysis of the data with regard to hypotension two subgroups evolved in the study group. Ten of the twenty subjects in the study group had their spinal anaesthetic induced approximately 5 minutes (range 5-8 minutes), after ephedrine administration. In the other 10 subjects an interval of approximately 10 minutes (range 9-14 minutes) occurred between ephedrine injection and induction of anaesthesia. Thus the study group divides into '5 minute' and '10 minute' subgroups.

Table 3.8

The number of patients in each group in whom hypotension occurred. Hypotension was defined as a decrease in systolic blood pressure below 100mmHg or by more than 30% from baseline blood pressure

	CONTROL GROUP	**STUDY GROUP**	**STUDY GROUP** '5 minute'	**STUDY GROUP** '10 minute'
Hypotension	16	10	7	3
No hypotension	4	10	3	7

The two groups were compared in respect of the above by means of Fisher's Exact Probability Test.

- No statistical difference was found between the control group and the study group. The P value was 0,0958.
- No statistical difference was found between the control group and the '5 minute' subgroup. The P value was 0,6573.
- *A statistically significant difference was found between the control group and the '10 minute' subgroup.* The P value was 0,0147.

Table 3.9

The number of patients in whom delayed hypotension occurred. Delayed hypotension was defined as hypotension occurring more than 30 minutes after subarachnoid injection.

	CONTROL GROUP	STUDY GROUP
Delayed hypotension	10	2
No delayed hypotension	10	18

The two groups were compared in respect of the above by means of Fisher's Exact Probability Test. *A statistically significant difference was found.*

The P value was 0,0138.

Table 3.10

The raw data and mean values for the lowest recorded systolic blood pressures occurring in patients from the two groups.

	CONTROL GROUP	STUDY GROUP
1	64	101
2	121	95
3	94	100
4	93	113
5	82	100
6	109	103
7	106	122
8	98	117
9	88	114
10	91	83
11	100	112
12	83	107
13	76	110
14	83	88
15	92	90
16	76	80
17	92	91
18	96	93
19	82	83
20	49	82
Mean	89	99
Standard deviation	15.8	12.8

The raw data, mean and standard deviations are listed in Table 3.10 and shown as a bar chart for emphasis in Figures 3.2 and 3.3.

The two groups were compared in respect of the above by means of the Student's t-test. *A statistically significant difference was found.* The P value was 0,034 (t value of 2,199).

Figure 3.2

A bar chart of the mean values of the lowest systolic blood pressures for the control and study groups.

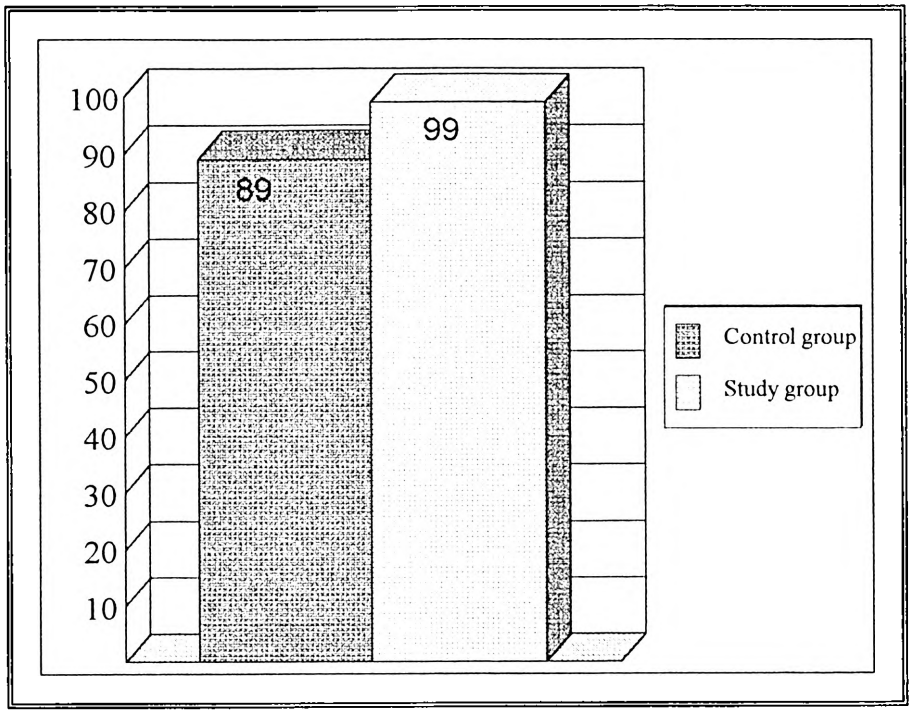
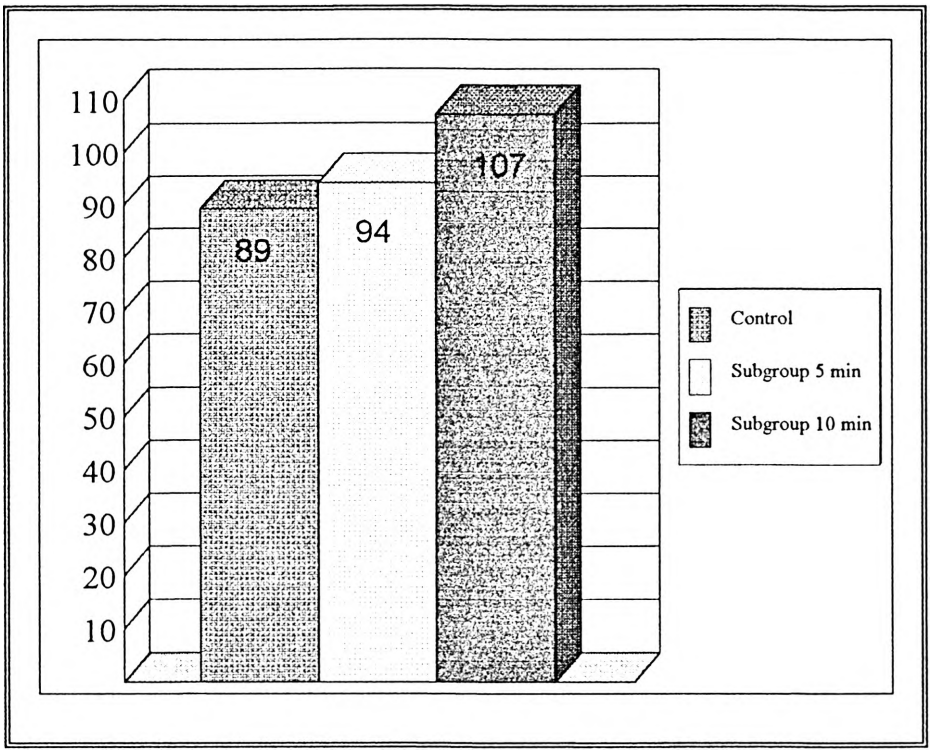


Figure 3.3

A bar chart of the mean values of the lowest systolic blood pressures for the control group and the two study subgroups.



The values for the mean lowest systolic blood pressure for the two subgroups are as follows -

'5 minute' subgroup: 94 (sd 11,9)

'10 minute' subgroup: 107 (sd 13,3)

The groups were compared in respect of the above by means of the Student's t-test.

- No statistically significant difference was found between the control group and the '5 minute' subgroup. The P value was 0,2654 (t value of 1,13).
- *A statistically significant difference was found between the control group and the '10 minute' subgroup.* The P value was 0,0007 (t value of 3,68).
- *A statistically significant difference was found between the '5 minute' and the '10 minute' subgroups.* The P value was 0,0476 (t value of 2,13).

3.5 FOETAL CONDITION

3.5.1 Umbilical venous blood gas and acid base analysis

Data sets were not complete in all cases. Two subjects from the study group were removed from analysis because of errors arising from malfunction of the blood gas analyser.

Table 3.11

The values for umbilical venous pH, pCO_2, pO_2 and HCO_3 for the two groups and the values for pH for the two subgroups.

Umbilical venous	CONTROL GROUP	STUDY GROUP	5 minute subgroup	10 minute subgroup
pH	7,35 (sd 0,05)	7,31(sd 0,06)	7,30(sd 0,03)	7,33(sd 0,02)
pCO_2	38,8 (sd 5,1)	40,25(sd 5,7)		
pO_2	23,8 (sd 7,8)	25,5(sd 6,3)		
HCO_3	21,2 (sd 2,6)	20,05(sd 2,2)		

The groups were compared in respect of pH by means of the Student's t-test.

- A statistically significant difference was found between the control group and the study group. The pH in the study group was lower. The P value was 0,0424 (t value of 2,11).
- A statistically significant difference was found between the control group and the '5 minute' subgroup. The pH in the '5 minute' subgroup was lower. The P value was 0,0091 (t value of 2,8).
- No statistically significant difference was found between the control group and the '10 minute' subgroup. The P value was 0,3046 (t value of 1,05).

The groups were compared in respect of the other blood gas variables (pCO_2, pO_2 and HCO_3) by means of the Student's t-test. No statistically significant differences were found. The P values were as follows-

- pCO_2, P=0,4260 (t value of 0,81)
- pO_2, P=0,4860 (t value of 0,70)
- HCO_3, P=0,1521 (t value of 1,46)

3.5.2. Apgar scores

The mean Apgar scores for the two groups at 1 minute and 5 minutes are as follows -

- Control Group 9 + 10
- Study Group 9 + 10.

3.6 COMPLICATIONS

There was no significant difference between the groups in the incidence of nausea, vomiting and pain. Six patients, three in each group, complained of nausea intraoperatively. Transient hypotension had occurred in 5 of those patients. No patient complained of discomfort or pain intraoperatively.

The average blood loss per patient was estimated at 500mls for both groups.
The average volume of intravenous Ringer's lactate solution used per patient was 1300mls for both groups.

3.7 NULL HYPOTHESES -CONCLUSIONS.

- The Null hypothesis which stated that an intramuscular bolus of 37,5mg of ephedrine causes no significant maternal hypertension and tachycardia, is supported.
- The Null hypothesis which stated that a intramuscular bolus of 37,5mg of ephedrine causes no significant foetal acidosis is supported for the subgroup in which a 10 minute interval between ephedrine injection and spinal induction occurred.
- The Null hypothesis which stated that an intramuscular bolus of 37,5mg of ephedrine does not reduce the incidence or severity of hypotension following spinal anaesthesia is rejected for the subgroup in which a 10 minute interval between ephedrine injection and spinal induction occurred.

CHAPTER 4

DISCUSSION AND CONCLUSIONS.

4.1 GENERAL REMARKS.

This study was undertaken to test the validity of the statement 'the prophylactic administration of intramuscular ephedrine prior to spinal anaesthesia is not to be recommended' [2].

The safety and efficacy of intramuscular ephedrine in the context of spinal anaesthesia in obstetrics have not been well documented. To the candidate's knowledge, only one controlled study has been published. As discussed in Chapter 1, that study, by Gutsche, was small (n=17) and could be faulted for using a pharmacologically active agent (procaine, with a known vasodilator effect) as placebo [9]. In spite of this, on the basis of that study, the technique continues to be recommended by contemporary text books [12]. Doses of 25mg or 50mg are suggested. No specific reference is made to the interval between ephedrine administration and the induction of spinal anaesthesia.

This is the first study to compare the efficacy and safety of prophylactic intramuscular ephedrine in spinal anaesthesia for Caesarean section with a true placebo. It is the first study in obstetrical anaesthesia to use a dose of 37,5mg of ephedrine intramuscularly and it is also the first study to comment on the influence of the time interval between ephedrine administration and spinal induction on the efficacy and safety of the technique.

The two groups in the study were well matched as to demographic criteria. All the subjects presented for the same surgical procedure in the same hospital but were operated on by different surgeons. All of the spinal inductions were carried out by the candidate. Interfering variables were reduced to a minimum. The average sensory level, assessed 20 minutes after induction of anaesthesia, was T2 (Gutsche recommends a sensory blockade to the level of T2 to avoid the visceral discomfort associated with traction on the peritoneum) [40].

4.2 HYPERTENSION.

The major concern regarding intramuscular ephedrine has been its association with persistent reactive hypertension. This study was designed to address this concern. Reactive hypertension related to vasopressor use was first documented in 1962 after a cerebrovascular accident was causally linked to the administration of a combination of an intramuscular alpha stimulant and an ergot alkaloid [6]. More recently, in 1982, an unacceptable level of hypertension was found when intramuscular ephedrine was used in epidural anaesthesia (a 75% incidence of significant hypertension associated with 50mg of intramuscular ephedrine) [1]. Hypertension was defined as an increase in systolic blood pressure of greater than 30% above baseline. In 1992 Rout et al. demonstrated reactive hypertension in patients given intramuscular ephedrine prior to general anaesthesia [2]. In their study 90% of patients who received 50mg of ephedrine increased their blood pressures by more than 20%.

This study in spinal anaesthesia detected a substantially lower incidence of hypertension than the above studies did. It found no increase in either the incidence or the severity of hypertension (defined as 30% above baseline) in the study group compared to the control group. The incidence of hypertension in the study group was only 30% which was not significantly higher than that in the control group (20%) (P=0,716). No other evidence of significant hypertension was found. The mean highest blood pressure in the study group was 153mmHg (sd 11,2) compared to 150mmHg (sd 12) in the control group (not significant P=0,419). There was no difference between the groups in mean blood pressure taken immediately before induction of spinal anaesthesia or immediately after delivery of the baby.

No significant incidence of persistent post-operative hypertension was detected in the study group. Only one patient in that group was found to be hypertensive post-operatively. This was in contrast with the finding in the above mentioned study in epidural anaesthesia, of an incidence of persistent hypertension of 66% [1]. Haemodynamic changes caused by ephedrine in epidural or general anaesthesia cannot be equated with those in spinal anaesthesia.

4.3 TACHYCARDIA.

The study detected a high incidence of tachycardia in both the control group and the study group. Tachycardia was defined, for the purposes of the study, as a heart rate of greater than 120 beats per minute. The incidence of tachycardia in the study group was 70% which was however, not significantly higher than that in the control group (65%) (P=1,00).

There was no evidence that the intramuscular technique resulted in significantly higher pulse rates than the intravenous bolus technique. The mean of the highest pulse rates in the study group was 130 (sd 21,4) beats per minute which was not significantly higher than that of the control group which was 123 (sd 20,5) beats per minute (P=0,293). The mean of all pulse rates in the first 30 minutes was 96 (sd 16,6) beats per minute for the study group compared to 92 (sd 13,8) beats per minute for the control group (not significant P=0,413).

4.4 HYPOTENSION.

With regard to efficacy in preventing hypotension, Gutsche had previously demonstrated a reduction in the incidence of hypotension from 100% to 25% with 50mg of intramuscular ephedrine [9]. The definition of a hypotensive episode, in this study, coincides with that of the majority of previous studies i.e. a decrease in systolic blood pressure of greater than 30% from baseline or a decrease in systolic blood pressure to below 100mmHg.

In this study the incidence of hypotension in the study group (50%) was less but not significantly less than that in the control group (80%) (P=0,0958). However, differences between the groups in terms of severity of hypotension did achieve statistical significance. The mean lowest systolic blood pressure in the study group was 99mmHg (sd 12,8) which differed significantly from that of the control group which was 89mmHg (sd 15,8) (P=0,034). The mean systolic blood pressure in the study group dropped by

19,5% (from 123mmHg to 99mmHg), whereas that of the control group dropped by 28,8% (from 125mmHg to 89mmHg).

The most notable effect of intramuscular ephedrine was demonstrated when a '10 minute' subgroup, as defined by the interval between ephedrine administration and subarachnoid injection, was separated from a '5 minute' subgroup. The cardiovascular stability of subjects in the '10 minute' subgroup was noteworthy. The incidence of hypotension was only 30%. The mean lowest systolic blood pressure was 107mmHg (sd 13,3) reflecting a reduction in mean systolic blood pressure of only 13% (from 123mmHg to 107mmHg) i.e. significantly less frequent (P=0,0147) and less severe (P=0,0007) hypotension than was found in the control group.

Considerable cardiovascular instability was evident in the '5 minute' subgroup. The incidence of hypotension was 70% which was not significantly different to that in the control group (80%) (P=0,6573). The mean lowest blood pressure was 94mmHg (sd 11,9) (i.e. a decrease of 24%), which also was not significantly different to that in the control group (P=0,2654). One patient in the '5 minute' subgroup required 15mg of intravenous 'rescue' ephedrine after a precipitous fall in blood pressure. She developed a severe tachycardia (170 beats per minute) and although her baby was clinically healthy, analysis of umbilical venous blood revealed evidence of possible transient asphyxia (pH 7,1).

These findings confirm the efficacy of 37,5mg of intramuscular ephedrine but mandate a minimum time interval between ephedrine injection and spinal induction of 10 minutes.

Another important finding was that of a low incidence of post-operative or delayed hypotension in subjects in the study group. Delayed hypotension was defined for the purposes of the study as hypotension occurring more that 30 minutes after induction of spinal anaesthesia. The incidence of delayed hypotension (requiring intravenous ephedrine boluses) was 50% in the control group compared to only 10% in the study group (P=0,0138) i.e. intramuscular ephedrine provides more sustained cardiovascular support than intravenous ephedrine. Intramuscular ephedrine may be particularly

advantageous where post-operative monitoring may not be reliable and where post-operative hypotension may go undetected.

4.5 FOETAL WELLBEING AND NEONATAL OUTCOME.

As discussed in the introduction, intramuscular ephedrine has been associated with abnormalities in foetal gas exchange [1,2]. It is well known that the uterine vascular bed has a high adrenoreceptor density which renders uteroplacental blood flow potentially vulnerable to vasoconstriction induced by alpha-adrenergic agonists. Ephedrine, although causing less vasoconstriction than pure alpha-agonists, does have a dose related alpha effect.

Both Rolbin and Rout have demonstrated dose related deterioration in foetal gas exchange with intramuscular ephedrine used in an epidural and general anaesthetic context respectively. Rolbin et al. showed an umbilical venous pH of 7,31 in their 50mg intramuscular ephedrine group and Rout et al., a pH of 7,24. Their patients' umbilical artery pHs were 7,18 and 7,16 respectively. Apgar scores were normal in both studies and neurobehavioural scores were normal in the Rolbin study. In contrast, neither Ward nor Gutsche found any adverse effect on foetal gas exchange associated with 50mg intramuscular ephedrine in epidural or spinal anaesthesia [9,29].

This study did detect a decrease in umbilical venous pH in the intramuscular ephedrine group, which may have been dose related. Since the primary focus of this study was on maternal haemodynamics, only umbilical venous blood was collected so that gross biochemical derangement in the foetus could be excluded. The mean umbilical venous pH of subjects in the control group was 7,35 (sd 0,052) and that of subjects in the study group 7,31 (sd 0,065) (significant P=0,0424).

Of interest, however, was an analysis of the data in terms of the '5 and 10 minute' subgroups mentioned previously. The mean umbilical vein pH of subjects in the '10 minute' subgroup of the study group was 7,33 (sd 0,02) which is not significantly lower than that of the control group (7,35 sd 0,052) (P=0,3046). The mean umbilical vein pH

of subjects in the '5 minute' subgroup was 7,30 (sd 0,03) which was significantly lower than that of the control group (7,35 sd 0,052) (P=0,0091) i.e. the decrease in pH may be a dose related phenomenon as subjects in the '5 minute' subgroup received considerably more intravenous 'rescue' ephedrine (130mg), than subjects in the '10 minute' group (20mg). Although subjects in the control group were given relatively large amounts of intravenous 'rescue' ephedrine, the total dose received (385mg) was substantially less than that in the study group (900mg, of which only 150mg was given as 'rescue' treatment).

There were no differences between the groups in any of the other cord blood gas variables i.e. pO_2, pCO_2, HCO_3. There were no detectable clinical consequences of the lower venous pH values in the study group i.e. Apgar scores were all above 8. It should be noted that although there were statistically significant differences between the groups, all pH values were within normal reference ranges [41].

The above findings reinforce the need for a minimum time interval of 10 minutes between ephedrine injection and spinal induction, and the use of the lowest effective dose of ephedrine possible. Data from this study suggests that 37,5mg is an adequate maximum dose for intramuscular administration (to replace the current recommended maximum dose of 50mg).

4.6 CONCLUSIONS.

Based on the findings of this study, the candidate recommends the following guidelines for the use of prophylactic intramuscular ephedrine:

- 37,5mg should be considered the maximum dose
- the time interval between intramuscular ephedrine administration and induction of spinal anaesthesia should never be less than 10 minutes
- for optimal effect, the technique should be combined with fluid preloading and left lateral tilt

- the technique should be used only by practitioners experienced in spinal anaesthesia and only in patients where no difficulty in administering the spinal is anticipated
- the technique has application mainly in non-labouring patients.

In conclusion, the findings of this study suggest that ephedrine administered in the above manner is effective in preventing hypotension and is safe from a maternal haemodynamic point of view. As regards the foetus, the question as to whether transient exposure to ephedrine is more or less dangerous than transient hypotension was not specifically addressed by this study. Although no deleterious effect to the foetus was detected when ephedrine was given 10 minutes prior to induction, this question remains a subject for future research in which more specific parameters of foetal response could be used.

Although it is self evident that intramuscular administration provides less predictable plasma levels of ephedrine than intravenous, the study showed that levels achieved provide safe and effective cardiovascular support. A future pharmacokinetic study of intramuscular ephedrine could reinforce the candidate's clinical observations. In a busy operating theatre environment of limited resources such as the one at Baragwanath Hospital, the intramuscular administration of ephedrine has specific utility in its economy of effort and equipment and offers the considerable advantage of sustaining blood pressure well into the post-operative period.

The recommendation of Rout et al. in 1992 was that intramuscular ephedrine be avoided in obstetrical spinal anaesthesia [2]. As discussed in the introduction, the evidence on which this recommendation is based is not, in the candidate's view, convincing. This is a time honoured and effective technique which should not be discarded by the anaesthesia community without good reason.

APPENDICES

Appendix A Patient Information Sheet

Appendix B Patient Consent Form

Appendix C Blood Pressure Chart

Appendix D Maternal Condition Form

Appendix E Foetal Condition Form

SUBJECT INFORMATION SHEET

BACKGROUND:

We intend using spinal anaesthesia for your Caesarian Section. Spinal anaesthesia is very popular because of it's safety and because it allows the mother to be aware of her babies' birth.Spinal anaesthesia is given by a simple injection in your back.

A common problem with spinal anaesthesia is hypotension (low blood pressure). We treat hypotension by giving fluids by means of a drip and by using a drug named ephedrine.

We are asking you to participate in a research study which will help us to learn whether, if the ephedrine is given before the spinal is done, we can **prevent** the problem of hypotension (low blood pressure).

PROCEDURE:

You will have your blood pressure checked on arrival in theatre. You will then be given an injection of either ephedrine or an inactive substance named normal saline. (For the purposes of the research, neither you nor the supervising doctor will know which injection you have been given.) Shortly thereafter the spinal anaesthetic will be given and the Caesarian Section performed. You will have your blood pressure repeatedly checked before, during and after the Caesarian Section.

POSSIBLE RISKS:

- If you receive the ephedrine injection you may develop brief hypertension (high blood pressure) which has **not** been shown by previous use of this drug to be dangerous and which, if neccesary , may be treated.

- If you receive the normal saline injection you may develop brief hypotension (low blood pressure) which we will treat with ephedrine given into the drip.

BENEFITS:

- **all** patients will benefit by receiving the best anaesthetic technique available for Caesarian Section.

- if you receive the **ephedrine** injection before the spinal you may experience less blood pressure instability.

- your participation will help to give our mothers better care in the future.

APPENDIX B

CONSENT TO PARTICIPATE IN EPHEDRINE TRIAL

PATIENT:

I agree to take part in the trial.

I have been given an explanation of the nature and purposes and possible hazards of the trial.

I confirm that I have informed the supervising doctor of any illness I may suffer from or of any drugs that I may be using.

I agree to co-operate fully with the supervising doctor and will report any unusual symptoms to him.

I am free to refuse to participate or to withdraw my consent and discontinue my participation in the study at any time and receive the normal treatment neccessary.

NAME: S. Dlamini

SIGNATURE: S. Dlamini

DATE: 22/5/96

SUPERVISING DOCTOR:

I confirm that I have explained the nature, purpose and possible hazards of the trial to the patient.

NAME: A. WEBB

SIGNATURE:

DATE: 22/5/96

WITNESS:

WITNESS:

EPHEDRINE TRIAL - BP CHART

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Systolic BP																				
Diastolic BP																				
Mean BP																				
Pulse rate																				
Ephedrine prn																				

	21	22	23	24	25	26	27	28	29	30	35	40	45	50	55	60	65	70	80	90
Systolic BP																				
Diastolic BP																				
Mean BP																				
Pulse rate																				
Ephedrine prn																				

EPHEDRINE TRIAL - Maternal condition Case no:
Name: _____ No.:_____Date:_____

Age: _____ Weight: _____ Height:: _____

Indication for Caesarian section:_____

Relevant history and examination: _____

_____

Injection level:_____ Sensory level:_____

Fluids : pre-spinal_____ Blood loss: _____
post-spinal_____
total_____

Intra-operative symptoms: nausea _____
vomiting_____
pain_____

Uterus: In/ Out

Times:IM injection_____
Spinal injection_____
Skin incision _____
Uterine incision_____
Delivery _____
Final skin suture _____

Baseline BP: Systolic _____ Diastolic:_____
Mean:_____ Pulse: _____

Threshold: _____ Assistant:_____

EPHEDRINE TRIAL - Foetal condition Case no:

Name: _____

Weight: _____ Premature/ Term

APGAR (pulse, respiration, colour, tone, reflex irritability)
1 min: _____
5 min: _____

Blood gas analysis:

Umbilical venous: pH _____
pCO2_____
pO2_____
HCO3_____
SBE_____
Sat._____

Other:_____

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