VASOPRESSORS FOR SUB-ARACHNOID ANAESTHESIA IN OBSTETRICS

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Despite recent studies[1] which suggest that spinal anaesthesia may not be the safest option for the fetus when caesarean section is required, it has, for many years, been the preferred technique for the majority of anaesthetists[2]. This is primarily due to the benefits conveyed to the mother. There are, however, a variety of complications and side effects associated with central neuraxial blockade in the pregnant patient, the commonest being maternal hypotension which is believed to occur in up to 95% of patients[3,4,5]. How important is this, and what should we be doing to prevent it?

Severe maternal hypotension gives rise to a reduction in utero-placental perfusion resulting in fetal bradycardia and acid-base abnormalities[6,7] and if prolonged, may lead to neurobehavioural changes in the newborn[8]. Although it has been suggested[9] that the duration of the period of hypotension is as important as the actual numerical value and, if transient, may be of little consequence, this concern indicates that it should be avoided or promptly treated. In the mother, hypotension leads to reduced cerebral blood flow which is associated with light-headedness and nausea and vomiting[10] . This, alone, may cause great discomfort and spoil what should be one of the most pleasurable experiences for the patient. Good control of the maternal systolic blood pressure will minimise, or even abolish, these unpleasant side effects[11,12].

Causes of hypotension

Spinal anaesthesia adequate for caesarean section will provide sympathetic nerve blockade up to T5 causing a fall in systemic vascular resistance (SVR). The normal reaction to this, in order to minimise the ensuing hypotension, is a reflex increase in heart rate and cardiac output. Denervation of the splanchnic autonomic ganglia (T5-11), however, also causes a significant venodilatation of the mesenteric bed with an increase in venous capacitance. This reduces the venous return to the extent that the reflex increase in cardiac output may be compromised or even abolished. These factors are compounded by the reduced venous return attributable to aorto-caval compression in the third trimester of pregnancy.

Spinal anaesthesia extending above T4 directly affects the cardiac sympathetic innervation, thereby attenuating the compensatory tachycardia and so a high spinal block may further reduce the heart rate.

Harrop-Griffiths[13] has suggested that another reflex (Bezold-Jarisch) may contribute to episodes of maternal hypotension in this setting. This reflex involves baroreceptors, in an under filled left ventricle, mediating a neural response which leads to increased parasympathetic activity over-riding the sympathetic tone. This reflex (although not fully understood) may explain why vasopressors and anticholinergic agents sometimes do not produce the expected results and also may explain the bradycardia seen in mothers in whom the spinal block is well below the T3-5 dermatomes.

Avoidance of hypotension

If no preventative measures are taken during caesarean section under spinal anaesthesia, the incidence of hypotension is reported as 92%[14]. Conservative measures include the avoidance of aorto-caval compression (left lateral tilt), and intra-venous fluid "pre-loading".

Aorta-caval compression does not only reduce maternal venous return and intervillous blood flow[15], but it also increases the spread of the spinal block, thereby compounding the issue. The deleterious effects of this have been recognised for many years and numerous papers have been published suggesting the degree of lateral tilt required to minimise them[16]. Although the majority recommend a 15 degree tilt to the left, this may prove to be inadequate and 20 degrees, or greater, may be required[17]. (It is recognised that anaesthetists are poor judges of the degree of tilt of the patient and frequently overestimate it [18]!) A full lateral position is much more effective than the lateral tilt in preventing hypotension[19] but only serves to delay its onset until the patient is repositioned for surgery.

As the reduction in cardiac preload due to mesenteric venodilatation is the root cause of the hypotension, it would appear logical to prevent this by expanding the circulating blood volume. Despite the fact that preloading the circulation with intra-venous fluids increases the cardiac output[20], its effects on maternal blood pressure are unreliable. However, colloids have been shown to be more effective than crystalloids when combined with leg wrapping[21]. There is, nevertheless, little evidence to suggest that either fluid type improves fetal well being, and some authors do not recommend their routine use[22]

Even with the careful use of these conservative measures, the incidence of hypotension may remain as high as 80-95%. To significantly improve this, vasopressors are indicated.

Vasopressors

Pressor agents raise the blood pressure, usually by vasoconstriction but also by increasing cardiac output. Vasoconstriction may be the result of central stimulation, direct action on the smooth muscle of the arterioles or venules, or by stimulation of the adrenergic receptors. In practice, the most commonly used drugs are the sympathomimetic agents which exert their effects via the adrenergic receptors. These may act ***directly*** on the receptor or ***indirectly*** by inducing the release of noradrenaline which then acts on the receptors. Because of their mode of action the indirectly acting drugs may exhibit tachyphylaxis (decreasing effect with repeated doses) on repeated administration.

The adrenergic receptors can be divided into alpha and beta (and dopaminergic) which are then further divided into sub-types 1 and 2. Alpha-1 receptors are distributed throughout the vascular smooth muscle and stimulation of them causes vasoconstriction. The alpha-2 receptors are located in the central nervous system and may cause sedation and analgesia. Beta-1 receptors are present in the heart and stimulation of them produces positive inotropic and chronotropic effects whereas beta-2 receptors are found in the bronchi, vascular smooth muscle and myometrium all of which are relaxed on stimulation. Stimulation of alpha-1 and beta-2 receptors will, therefore produce opposing effects on the vasculature smooth muscle.

Phenylephrine is a direct acting, potent alpha-1 agonist with no beta activity. It, therefore, causes a rapid increase in systemic vascular resistance and blood pressure. Metaraminol exhibits both direct and indirect activity. It has some beta activity but acts predominantly via the alpha-1 receptors so also increases systemic vascular resistance. Ephedrine is a potent alpha and beta agonist, acting both directly and also indirectly. Its effects on vascular resistance are less pronounced than the other alpha agonists but it also increases cardiac output thereby maintaining blood pressure.

Ephedrine was introduced into Europe in 1923 and by 1927 was being used to treat the hypotension associated with spinal anaesthesia. There was, however, a great reluctance to use vasopressors in the pregnant patient due to their effects on the uterine artery and Crawford (1966), and others[23,24], thought that the maintenance of maternal blood pressure by the action of vasopressors was responsible for foetal asphyxiation. Evidence supporting the use of ephedrine, however, came from the seminal paper by Ralston & Shnider (1974) in which uteroplacental blood flow (UBF) and fetal acid-base status were measured in pregnant ewes following the administration of equipotent doses of ephedrine, metaraminol, mephentermine and methoxamine[25]. When given in sufficient dose to raise the maternal arterial pressure by 50%, ephedrine had little effect on UBF and fetal arterial pH whereas the alpha-agonists caused a marked reduction in UBF. This study led clinicians to believe that ephedrine was the most efficacious agent in the prophylaxis and treatment of maternal hypotension for over 30 years. There are now, however, doubts about the relevance of this paper to humans. Quite apart from the inter-species variation, the ewes were studied in the standing position, were not anaesthetised and were rendered hypertensive by the infusion of vasoconstrictors. The animals also received doses of alpha-agonists greater than those used in clinical practice!

The fall in arterial pressure following spinal anaesthesia is caused partly by a reduction in systemic vascular resistance (SVR) but, predominantly by a reduction in cardiac output secondary to venodilatation and a decreased venous return. Pure alpha-agonists will correct the fall in the SVR and prevent venodilatation, thereby maintaining cardiac preload and output and preserving arterial pressure. A combined alpha- and beta- agonist has a lesser effect on SVR and venous capacitance so the patient remains vasodilated and venous return is reduced. Cardiac output, however, may rise following beta- mediated increases in myocardial contractility and heart rate, offsetting the fall in SVR.

These responses have been identified in clinical practice[26] and subsequently repeated in numerous studies. Following epidural anaesthesia for caesarean section, minimal changes in SVR were measured but there was a significant reduction in end diastolic volume leading to a compensatory tachycardia. Both ephedrine (alpha and beta agonist) and phenylephrine (alpha-agonist) corrected the fall in arterial pressure and maintained cardiac output at pre-epidural levels. Ephedrine, however, achieved this at the expense of an increase in heart rate whereas phenylephrine returned the heart rate to pre-epidural levels, suggesting that it is better at maintaining pre-load and stroke volume. Capacitance vessels in the splanchnic bed are more sensitive to vasoconstrictors than resistance vessels[27] so it is possible that careful use of low dose alpha-agonists may regain the majority of capacitance function, before there is a significant increase in vascular resistance, thereby preventing uterine vasoconstriction. These investigations support the theory that alpha-1 agonists should be superior to mixed alpha and beta agonists in preventing hypotension following spinal anaesthesia. They, therefore, should improve the condition of the mother but does this necessarily imply that they will improve the condition of the fetus?

The mature placenta is a high capacitance, low pressure organ with no autoregulatory and little vasoconstrictor

ability[4]. Pregnancy is associated with a reduced response to alpha- agonists particularly in the uterine arterioles[28]. Further studies on pregnant ewes[29] demonstrated that a gradual occlusion of the uterine arteries failed to produce fetal acidosis until the blood flow was reduced by over 60%. Uteroplacental perfusion pressure should, therefore, be dependant on the systemic arterial pressure.

Currently accepted signs of foetal compromise are, unfortunately, inadequate and unreliable. Though prevention of hypotension with phenylephrine has been shown to produce a higher umbilical artery(UA) pH than with ephedrine[30] this reflects both metabolic and respiratory acidosis, the latter of which may occur without fetal hypoxia. The more relevant measurement of standard base deficit, indicative of prolonged hypoxia, does correlate with neonatal outcome, but only at a magnitude unlikely to be seen in comparative studies. Doppler studies (pulsatility index) do not actually measure fetal well being or uteroplacental blood flow, but vascular resistance in the distal uterine bed which is dramatically affected by the physiological changes following spinal anaesthesia[31] and, therefore, subject to great variation. Apgar scores are highly subjective and poor predictors of neurological outcome and fail to demonstrate a correlation with maternal blood pressure. We cannot, therefore, be absolutely confident about the effects of drugs on the fetus!

A survey of obstetric anaesthetists practicing in the UK showed that over 95% still use ephedrine as their vasopressor of choice in caesarean sections[32]. This would suggest that, despite recent evidence to the contrary, they still are concerned about the potential effects of other agents on uterine blood flow. Both ephedrine and the alpha-1 agonists would appear to be **relatively** effective in maintaining maternal arterial pressure and many studies report there to be no significant difference in fetal outcomes when comparing the use of the various agents. Meta-analysis, however, has shown that ephedrine is associated with a more severe umbilical artery acidosis than the alpha- blockers phenylephrine and metaraminol, although this is inconclusive evidence with regard to the foetal compromise (vide supra).

This acidosis may be associated with an increase in umbilical arterio-venous CO_2 difference, suggesting an increase in fetal metabolic rate by direct beta-adrenergic stimulation[33]. Ephedrine readily crosses the placenta and fetal blood concentrations are approximately 70% of maternal. This has been associated with an increase in fetal heart rate and beat-to-beat variability[34]. Excessive administration is also associated with serious maternal cardiac arrhythmias particularly in the presence of a high spinal block and increased vagal tone.

Phenylephrine, while as effective as ephedrine in restoring maternal arterial pressure, does not affect the fetal circulation although it may cause a reflex bradycardia in the mother. Atropine rapidly restores the maternal heart rate without inducing a tachycardia, but this, itself crosses the placenta and may affect fetal haemodynamics[35]. A more suitable alternative may be glycopyrralate which has a more prolonged effect without crossing the placenta. Both of these anticholinergic agents may also reduce the incidence of nausea in the mother.

As the diagnosis of hypotension is retrospective, should we be administering vasopressors prophylactically to prevent rather than treat? Disadvantages of this are causing hypertension when the expected fall in pressure does not occur and inducing tachyphylaxis when using ephedrine. The response times to boluses of either phenylephrine (27s) or ephedrine (78s) is sufficiently rapid to warrant prophylactic treatment unnecessary[36] although the former would appear to be superior in its onset of action. Neither intramuscular nor intravenous ephedrine , when given prophylactically, demonstrate an improvement in neonatal outcome compared with their use in treating, and are not recommended[5].

In the absence of recognised vasopressors, alternative strategies must be used to minimise the fall in maternal blood pressure. In many situations increasing fluid preload is preferred but this, as has been shown, has limited efficacy. Adrenaline is frequently used for maintaining blood pressure in the critical care situation. It does this by its potent action on alpha-1 and 2, and beta-1 and 2 receptors. In low doses the beta effects predominate causing an increase in cardiac output but with a fall in systemic vascular resistance. As the dose increases, so does the alpha-1 activity leading to a rise in vascular resistance and an increase in blood pressure. This, unfortunately, predisposes the patient to cardiac arrhythmias and the beta-2 effects may causes a reduction in uterine tone at a time when there is an increased likelihood of haemorrhage. Adrenaline is, therefore, not a particularly suitable drug for the maintenance of maternal blood pressure but may be used in the emergency situation when other methods have failed. The drug should be titrated to effect and may be injected in 0.3 - 0.5ml. aliquots of 1:10,000, but a safer technique is controlled infusion of a more dilute solution e.g. 1:20,000

Conclusion

There is no doubt that avoiding maternal hypotension, following spinal anaesthesia for caesarean section, is important for the well being of the mother and fetus.

The patient should be placed in the lateral position while establishing the block and returned to a left lateral tilt

position (using a wedge in preference to lateral table tilt) for surgery. Although there is little evidence for the use of an intravenous pre-load, an infusion of 1,000mls of crystalloid may be given either before administering the spinal or while waiting for the block to be established.

Blood pressure should be monitored at regular and frequent intervals. Falls in maternal systolic pressure below 100mmHg or greater than 15% of baseline should be treated with a vasopressor.

Ephedrine has been the vasopressor of choice for the last 30 years. Despite increasing evidence that alpha 1-agonists may be more effective and less harmful than was once believed, it remains so! There is probably little difference in the efficacy of the various alpha-1 agonists, and many have been tried, but due to the limited number now being manufactured, we are generally limited to a choice between phenylephrine and metaraminol.

Ephedrine, phenylephrine and metaraminol may all be used to maintain an adequate maternal blood pressure and uteroplacental perfusion following spinal anaesthesia. The choice is frequently made on the grounds of the maternal heart rate - those with a tachycardia are given phenylephrine or metaraminol, and those in whom the pulse is less than 60/min., ephedrine. Some regard ephedrine as the safer agent as it is the one with which we are most familiar and, along with metaraminol, require a simple dilution to 10mls. Phenylephrine, conversely, requires a double dilution technique or, alternatively, dilution to a large volume (both 100mls and 500mls have been recommended) which has led to confusion, errors and overdosage. On the grounds, however, that the alpha- agonists are more specific in their action on the splanchnic venous bed (the primary cause of the hypotension) and probably cause fewer biochemical disturbances in the fetus than ephedrine, we should, perhaps be reviewing our thoughts on this 30 year old habit and ensuring a scrupulous technique in our drug preparation and administration!

Case Report

A 35 year female, para 2+0, was admitted at 37 weeks gestation for elective caesarean section delivery of her twins. Early delivery had been agreed due to increasing discomfort from her large abdominal mass, marked peripheral oedema, varicosities on her legs and haemorrhoids. Her previous obstetric history consisted of a spontaneous vaginal delivery followed, two years later, by an emergency caesarean section, for acute foetal distress, under epidural anaesthesia. Apart from the symptoms caused by her pregnancy she was in good health with a normal blood pressure. Having discussed the options available she had decided upon spinal anaesthesia for the procedure.

Following oral premedication with ranitidine 150mg and metoclopramide 10mg, a 16G intravenous cannula was inserted in her left forearm and 1000mls Hartmann's Solution infused. Blood pressure (BP) and heart rate (HR) were measured at 130/80 mmHg and 90 beats/min. With the patient in the sitting position, and under aseptic conditions, a 25G pencil-point tipped spinal needle was inserted through the dura by a midline approach at the L3-4 interspace. Having confirmed free flow of CSF, a mixture of 2.2mls 0.5% hyperbaric bupivacaine and 300mcg diamorphine was slowly injected. On completion of the injection the patient was immediately placed in the supine position, with a right lateral tilt, for 2 minutes. Her BP and HR were measured immediately and at 2 minute intervals.

The recording at 2 mins was 110/75 and 95/min. She was then rolled over to a left lateral tilt position to minimise aorto-caval compression. At this point she began to complain of feeling "light-headed" and her BP/HR were found to be 95/75 and 85/min. Metaraminol 0.5 mg was administered IV, but the patient remained "light-headed" and now complained of feeling nauseated. BP/HR were 85/45 and 85/min. A further 1mg metaraminol was injected but the patient became pale and clammy and unwell. ECG showed a sinus bradycardia of 40 beats/min. with multiple ectopic beats although pulse oximetry showed oxygenation to be satisfactory.

The heart rate was restored with glycopyrrolate 0.2mg but the patient's condition did not improve until she was rolled into a complete left lateral position. She then felt significantly better and her recordings were 125/80 and 115 beats/min. The height of the block was assessed, initially by cold (ice cube) and found to be T6 bilaterally. To enable the surgeon to proceed, the patient was again repositioned (with lumbar wedge) into a 20 degree left lateral tilt (with side supports to prevent her from rolling off the table). Although no longer nauseated, she again began to feel "light-headed" not withstanding her BP/HR measurements of 110/65 and 100beats/min. It was suspected that despite the significant lateral tilt, her excessively large uterine contents were contributing to continuing aorto-caval compression.

It was found impossible to increase the tilt and still allow surgical access. A further increment of metaraminol 0.5mg increased the BP to 135/80 without affecting the heart rate and improved the patient's condition. The surgeon was informed of the situation and delivered twin 1 rapidly. At this point she again began to feel much better and her HR fell to 85/min. although her BP remained at 135/85. Twin 2 took a further 8 minutes to deliver but cardiovascular recordings remained stable throughout this period. Following delivery the operating table was restored to the level position with no untoward effect on the mothers comfort. Syntocinon 5iu was administered by slow intravenous injection followed by an infusion of 10 iu./hour for 4 hours. Blood pressure fell slightly to 110/75 with a significant fall in heart rate to 65/min. Apgar scores at 1 and 5 minutes were 9 and 10 for twin 1 and 7 and 10 for twin two. Umbilical cord pH's were not measured. Closure of the abdomen proceeded uneventfully.

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