Review Article

The role of vasopressors in the management of hypotension induced by spinal and epidural anaesthesia

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Although spinal and epidural blocks provide excellent anaesthesia for many operations, they are frequently accompanied by hypotension. This is largely the result of sympathetic nerve blockade. Excessive hypotension may potentially produce myocardial and cerebral ischaemia, and is associated with neonatal acidaemia in obstetric practice. How to prevent and treat this hypotension has been the subject of much investigation and controversy. One of the mainstays of management is the use of vasopressor agents and those currently available are not perfect. In this review, the role of vasopressor agents is discussed and possible future management strategies are commented upon. Ephedrine was the first agent used for this purpose and it has withstood the test of time: it is the agent against which all others are compared. It remains the first-line agent in obstetric anaesthesia as it does not affect the fetus adversely, but it cannot be relied upon to be 100% successful and other agents must be considered when it is inadequate. It is best given by infusion. In non-obstetric practice, ephedrine has a good track record but again its success rate is less than 100%. As there is no fetus to consider, it may be more appropriate to consider using a pure vasoconstrictor agent such as methoxamine or phenylephrine as a first-line therapy in such cases. This judgement can only be made on an individual patient basis as ephedrine produces a tachycardia while phenylephrine and methoxamine both produce bradycardia.

Bien que les blocs épidural et rachidien produisent une excellente anesthésie pour plusieurs interventions, ces deux techniques se compliquent fréquemment d'hypotension. Cette complication résulte principalement du blocage sympathique. L'hypotension peut provoquer de l'ischémie myocardique et cérébrale et, en obstétrique, de l'acidose néonatale. La prévention et le traitement de l'hypotension demeurent des sujets de recherche et de discussion. Le traitement de l'hypotension repose surtout sur l'utilisation de vasopresseurs dont aucun de ceux qui sont en usage actuellement n'est idéal. Ce survol porte sur le rôle des vasopresseurs et sur l'application de stratégies futures. L'éphédrine, le premier médicament utilisé à cet effet, a subi l'épreuve du temps et c'est à l'éphédrine que tous les autres vasopresseurs sont comparés. L'éphédrine demeure l'agent de choix en obstétrique parce qu'elle n'a pas d'effets nocifs sur le foetus. Elle n'est pas toujours efficace et il faut, au besoin, prévoir une autre médication. L'éphédrine est plus efficace en perfusion. En dehors de la pratique obstétricale, l'éphédrine a une bonne réputation mais son taux de succès n'atteint pas 100%. Lorsqu'un foetus n'est pas en cause, il semble préférable d'adminstrer un vasoconstricteur pur comme la méthoxamine ou la phényléphrine comme médicament de première ligne. Cette décision ne peut être prise que sur une base individuelle étant donné que l'éphédrine produit de la tachycardie alors la méthoxamine et la phényléphrine produisent de la bradycardie.

Key words

ANAESTHETIC TECHNIQUES, REGIONAL: spinal, epidural;
COMPLICATIONS: hypotension;
SYMPATHETIC NERVOUS SYSTEM: pharmacology, adrenaline, ephedrine, metaraminol, methoxamine, phenylephrine.

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Historical aspects

It was in 1885 that Leonard Corning, a New York neurologist, first produced epidural or subarachnoid anaes-

thesia when he injected cocaine into the spine of both a dog and a patient producing a block in the lower half of the body.[1] However, it took until 1898 for the technique to be first used for surgery by August Bier in Kiel, Germany. He soon abandoned the technique because of the toxicity of cocaine and its short duration of action. The development of procaine, a much safer agent, in 1904 by Einhorn enabled spinal anaesthesia to gain popularity. Later developments included the manufacture of amethocaine and cinchocaine. Lidocaine, the first amide local anaesthetic, was synthesised in 1943 by Nils Löfgren. This in turn led to the production of derivatives, including mepivacaine, prilocaine, etidocaine and bupivacaine.

Epidural block is a much newer technique.[1] The sacral route was described independently by Sicard and Cathelin in 1901, and first used for analgesia for childbirth by Stoeckel in 1909. The lumbar approach was apparently first described by Pages in Spain in 1921, but he died soon afterwards. It was a decade later that the approach was "rediscovered" and popularised by Dogliotti in Italy.

It soon became apparent that hypotension could be a major problem with both these techniques. The management of this problem therefore became important in order that the quality of anaesthesia produced by these blocks could be matched by safety. Methods developed for the management of the hypotension fall into four categories:

i Volume expansion
ii Physical methods to increase in venous return.
iii Prevention or treatment of associated bradycardia.
iv Vasoconstriction

These techniques have been used separately and in combination with varying degrees of success, and the optimal form of management remains the subject of much discussion.

(i) *Volume expansion*

It is common practice to infuse large volumes (10–20 $ml \cdot kg^{-1}$) of electrolyte crystalloid solution (e.g., saline 0.9%) rapidly to help prevent or to treat hypotension induced by a spinal or epidural block.[2] This will increase venous return and therefore cardiac output.[3–5] Haemodilution also occurs,[6,7] which will improve peripheral circulation, but this may be at the expense of oxygen delivery. The use of excessive volumes of crystalloid may therefore do more harm than good. Crystalloid preloading may also be relatively ineffectual in preventing hypotension.[8] A recent study[9] found that although preloading reduced the incidence of hypotension, there was still a considerable proportion of the patients who became hypotensive and the clinical relevance of the reduction in the incidence of hypotension is questionable. A further problem is the increased need for catheterisation as a result of developing urinary retention as a combined effect of the spinal block itself and the fluid load given. Large fluid loads may be poorly tolerated by patients with limited myocardial reserve or with a relatively fixed cardiac output because of valvular heart disease. Some of these problems may be lessened by the use of smaller volumes of colloid solutions,[10] but again this approach may not be completely successful, and colloid solutions have been known to produce anaphylactoid reactions in a small number of patients. It is therefore clear that intravenous fluids do not provide a complete solution to this problem.

(ii) *Physical methods to increase venous return*

Venous return can be augmented by elevating the patient's legs (providing the femoral veins remain unobstructed) or by the use of a head-down tilt. These manoeuvres alone may be sufficient to restore blood pressure to an acceptable level.[3] However, this is not always the case and other methods must then be used. The head-down position may also be regarded as undesirable when hyperbaric local anaesthetic solutions are used because of concern over cephalad spread of the block.

(iii) *Prevention or treatment of associated bradycardia*

Spinal blockade affecting the upper thoracic spinal cord segments (T_{1-3}) produces bradycardia by blocking the cardioaccelerator nerve fibres, allowing vagal tone to dominate. As heart rate is one of the determinants of cardiac output and hence blood pressure, drugs with vagolytic actions (e.g., atropine) can be used to elevate heart rate and hence blood pressure. However, the response is erratic and the disadvantages may outweigh the benefits. In particular, the production of a tachycardia is undesirable in patients dependent on heart filling and coronary perfusion during diastole.[3]

(iv) *Vasoconstriction*

Sympathetic blockade is produced by spinal and epidural blocks, resulting in vasodilatation. This may be corrected by the use of vasoconstrictor (vasopressor) agents. The remainder of this article examines the role of vasoconstrictor drugs in the management of this problem.

Physiology

It is important to understand the alterations in physiology produced by spinal blockade in order to make rational choices in managing the resulting hypotension.

Spinal or epidural block results in a number of changes in the cardiovascular system which may all contribute to the associated hypotension.[3,11] Essentially, all of the cardiovascular effects of spinal anaesthesia are mediated by blockade of the preganglionic sympathetic neurones produced when local anaesthetic is injected into the sub-

arachnoid space. Plasma concentrations of local anaesthetics used for spinal anaesthesia are too low to have any direct effect on the cardiovascular system. The main difference between the responses to spinal and epidural blockade seems to be the more rapid onset of changes with spinal anaesthesia, while the dose of local anaesthetic used in an epidural block is much greater. These may be summarised as follows.

1 *Reduction in vasomotor tone*
This results in arterial and arteriolar vasodilatation, as a direct result of the sympathetic neurone blockade, producing hypotension.[12] Compensatory vasoconstriction may occur in the upper part of the body above the block, as a result of baroreceptor activity. Consequently, those areas with intact sympathetic innervation may be shown to be vasoconstricted as demonstrated by a decrease in skin temperature[13,14] and a decrease in forearm blood flow.[15] As the upper arm blood flow is less than 5% of the cardiac output, the ability to compensate for vasodilatation in the lower body is limited. Cerebral vasoconstriction does not occur during spinal anaesthesia.

2 *Loss of cardioaccelerator nerve function*
Blockade above the T_5 level results in the removal of the chronotropic and inotropic influence of the sympathetic nervous system.[16,17] Peripheral venodilation also diminishes venous return, which contributes to the bradycardia. Cardiac output, and hence blood pressure, may therefore fall.

3 *Systemic uptake of local anaesthetic*
Equal doses of local anaesthetic administered into the subarachnoid and epidural spaces produce similar plasma concentrations of drug (75 mg lidocaine produce a plasma concentration of 0.32 ± 0.07 mg · ml^{-1} after subarachnoid injection versus 0.41 ± 0.07 mg · ml^{-1} after epidural injection),[18] but the aborption is more rapid from the epidural space, presumably because of its greater vascularity. The much smaller doses of local anaesthetic used for a spinal block can be expected to have little systemic effect, but the absorption of large doses from the epidural space may be considerable.[19] Local anaesthetics used intravenously for control of cardiac arrhythmias are known to cause myocardial depression[20] and it has been shown that epidural administration of such drugs will also produce plasma concentrations great enough for systemic effects to be produced (blood lidocaine concentrations have been measured at between 3 and 7 mg · ml^{-1}.[11] It has been shown that lumbar epidural anaesthesia (without blocking the cardioaccelerator fibres) can reduce cardiac output and arterial blood pressure. However, it has also been shown that local anaesthetics can produce positive chronotropic and inotropic effects, which may be centrally mediated.[21] The net effect therefore depends on the height of the block produced, as the cardioaccelerator fibres must remain intact for these stimulatory properties to be of relevance.

4 *The systemic effects of vasoconstrictors*
Adrenaline is commonly added to local anaesthetic solutions for epidural block. This is absorbed along with the local anaesthetic and can produce its own systemic effects. In a concentration of 1:200,000 (5 μg · ml^{-1}) the dose of adrenaline a patient receives for an epidural block will typically be 50–100 μg. This dose will produce β-adrenergic stimulation but not α-adrenergic stimulation.[22] It may therefore be expected to produce positive chronotropic and inotropic effects, while at the same time producing vasodilatation. It has been shown that in patients with equal levels of sensory block, less alteration of cardiovascular variables results from an epidural block with plain local anaesthetic than after a spinal block,[3] while those undergoing epidural block with adrenaline in the local anaesthetic solution experience a greater decrease in mean arterial pressure and total peripheral resistance, and a greater increase in heart rate, cardiac output and stroke volume than those who did not have adrenaline in their local anaesthetic.[3,23]

Because of the sometimes unwanted β-effects of adrenaline, phenylephrine, a drug with almost pure α-adrenergic activity has been studied as an alternative. This produced, as expected, an increase in peripheral resistance and hence blood pressure, but at the expense of a reduction in stroke volume (and hence cardiac output) and an increase in central venous pressure.[24]

5 *Patient factors*
If spinal anaesthesia is performed in a standardised manner on a large series of patients, keeping the height of block and position of the patient constant in all cases, some patients will show very little alteration in blood pressure while others will show pronounced hypotension. There may be many reasons for this variabilty in response, such as pregnancy,[3] old age, pre-existing hypertension or cardiovascular disease, and hypovolaemia. Patients with pre-existing hypertension undergoing spinal anaesthesia show a much greater decrease in blood pressure and peripheral vascular resistance than normotensive patients with equivalent levels of anaesthesia.[25] Age is a major factor in determining the haemodynamic response to spinal anaesthesia, the degree of hypotension increasing with increasing age.[26,27] The effect of co-existing medical disease on hypotension induced by spinal anaesthesia can also be shown to be of importance: patients in ASA class III may produce a more pronounced hypotensive response

than patients in ASA classes I or II.[28] Spinal anaesthesia in the presence of hypovolaemia may be associated with severe hypotension and cardiovascular depression,[29,30] and should be avoided in this situation whenever possible.

The "ideal" vasopressor agent

The "ideal" vasopressor agent will be one that is capable of reversing the adverse physiological changes outlined above without inducing its own adverse effects. Such an agent must therefore:

i be capable of constricting dilated vascular beds, and

ii possess positive inotropic and chronotropic properties.

It should not produce cerebral stimulation, and prolonged hypertension, outlasting the duration of the block, should not occur. It should not sensitise the myocardium to catecholamines or itself increase myocardial irritability. A desirable property for use in obstetric practice is that it should not cause uterine vasoconstriction. The uterine vessels possess only α-receptors[31] and so can only respond to sympathomimetic agents by constricting: administration of phenoxybenzamine (an α-adrenergic blocking agent) does not increase uterine blood flow, demonstrating that the uterine vessels are functioning at or near a state of maximum haemodynamic efficiency.[32] A further undesirable feature is the development of tolerance to the effects of the agent.

History of the use of vasopressor agents

Ephedrine was the first agent to be used successfully to treat hypotension induced by spinal anaesthesia, in 1927.[33] Later research examined the effects of other drugs, including paredrine, methedrine, pitressin-ephedrine combination,[34] and later methoxamine,[35,36] phenylephrine,[37,38] metaraminol, mephentermine,[39] dopamine[40,41] and dobutamine.[42]

Pharmacology

Ephedrine

This drug has both α- and β-adrenergic agonist actions. It is the active principle of the Chinese plant Ma Huang, used for centuries in the East. It was first brought to Europe in 1923 and it is now produced synthetically. It acts both directly and indirectly at adrenergic nerve endings, enhancing release of noradrenaline. It also inhibits monoamine oxidase (MAO). Tachyphylaxis is a marked feature.[43] It does not contain a catechol moiety and is active when given orally. It is excreted in the urine with a half-life of three to six hours. Structurally it has two asymmetrical carbon atoms: only l-ephedrine and racemic ephedrine are used clinically.[22]

Its effects on the cardiovascular system consist of an increase in heart rate and cardiac output. Vasoconstriction is almost balanced by vasodilatation, and peripheral resistance is usually little changed. Blood pressure is therefore usually increased, systolic more than diastolic. Myocardial irritability is increased, which may produce arrhythmias. Other actions include a reduction in cerebral and renal blood flow, bronchodilation (hence its use in treating asthma), increase in sphincter tone (which may lead to urinary retention). It is a potent cerebral stimulant, although not as potent as amphetamine.[22,43]

It is listed in Martindale's[44] as the sulphate, but no recommended dose is quoted for treating the hypotension of spinal or epidural anaesthesia. It is recommended in Goodman and Gilman that "the dose is titrated according to the response".[22] Doses commonly used are 3 to 10 mg *iv* or 15 to 30 mg *im*. It may be used as an infusion; for example, diluting 60 mg of ephedrine in one litre of a crystalloid solution and infusing at a rate titrated against the desired response.

Methoxamine

Methoxamine is a sympathomimetic agent with relatively specific direct actions at α_1-receptors. It produces some blockade of β-receptors. Its major effect on the cardiovascular system is to produce a rise in blood pressure as a result of peripheral vasoconstriction, with both systolic and diastolic blood pressures increased. There is no effect on myocardial contractility or irritability. Sinus bradycardia occurs, as a result of the activation of vagal barorecptor reflexes, although β-receptor blockade may play some part. Therefore, cardiac output is decreased. It has no effect on bronchial muscular tone, and does not stimulate respiration. It does not produce cerebral stimulation.[22,43] Its use is contra-indicated in patients with severe myocardial or coronary disease, and in patients taking monoamine oxidase inhibitors. It must also be used with extreme care in patients with hypertension or hyperthyroidism.[43] Methoxamine is presented in 1 ml ampoules containing 20 mg of the hydrochloride, which may be diluted before use. Quoted doses[22,44] are 2 to 5 mg by slow *iv* injection: it acts within two minutes and its effects last for up to an hour. Ten to 15 mg may be given *im*, although absorption from an *im* injection may be unreliable in the hypotensive patient: it takes up to 20 min to act, but then lasts somewhat longer. It may be used as an *iv* infusion at a rate of 5 $\mu g \cdot min^{-1}$.

Phenylephrine

Phenylephrine is a directly acting selective α_1-agonist: it activates β-receptors only at much higher concentrations. The l-isomer is the active form. It has little or no effect on cardiac output or force of contraction, but myocardial

irritability is slightly increased.[43] Bradycardia results from baroreceptor activation. Vasoconstriction leads to an increase in blood pressure. It has no cerebral actions. It may produce bronchodilation, but this is of little clinical value.[22,43]

Phenylephrine is presented in 1 ml ampoules containing 10 mg of the hydrochloride. Quoted doses are 2 to 5 mg by *im* or *sc* injection or 100 to 500 μg by slow *iv* injection.[22] This dose in practice seems to be far too high, with the production of severe hypertension in some cases.[45] When ephedrine has failed to increase blood pressure significantly, 20 to 40 μg of phenylephrine may be given. If this does not produce an adequate response, the dose may be increased (up to a maximum of 100 μg) or repeated. The total dose rarely exceeds 200 μg. The duration of action of a bolus is from two to five minutes. It may also, therefore, be used as an infusion: 10 mg phenylephrine in 500 ml glucose 5%, and the infusion rate is then titrated against the response.[43] As with methoxamine, phenylephrine should be avoided in patients with ischaemic heart disease or hypertension.[43]

Adrenaline

Adrenaline (epinephrine) is the predominant natural catecholamine secreted from the adrenal medulla, forming 80% of the total catecholamine content in adults, the remainder being noradrenaline. In infancy, however, noradrenaline is the major component.[43] Adrenaline is also found in some central nervous system neurones. Because of its prominent role in the body it has been extensively studied.

It is one of the most potent vasopressor drugs known. It has both α- and β-stimulating properties, and therefore will produce arteriolar and venous vasoconstriction. It has potent chronotropic and inotropic actions on the heart. Although heart rate is increased following administration, at the peak of the blood pressure rise transient bradycardia may be seen as a result of vagal discharge following baroreceptor stimulation. The effects of adrenaline on adrenoceptors is dose-dependent.[22] Minute doses (0.1 $\mu g \cdot kg^{-1}$) may cause a decrease in blood pressure due to peripheral vasodilatation. The β_2-receptors, which mediate vasodilatation, are more sensitive to adrenaline than to the vasoconstrictor α-receptors. Therefore, increasing the dose will produce a greater effect on the α-receptors in the peripheral circulation, with consequent vasoconstriction. Other effects include bronchodilation and cerebral stimulation.

It may be given by bolus slow *iv* injection (e.g., 0.1 mg), but its effects are short-lived. Therefore, it is usually given by infusion, beginning at a dose of 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

Metaraminol

Metaraminol has both α- and β-stimulating effects, with both direct and indirect modes of action. It therefore exhibits chronotropic, inotropic and vasoconstrictor actions. It has few other systemic effects.[43] It can be given by *sc*, *im*, or *iv* injection. Recommended doses are 0.5 to 5 mg *iv*[22] or 2 to 10 mg by *im* injection. When injected *iv* it acts in one to three minutes and lasts for about 25 min. When given *im* it acts in five to ten minutes, and lasts for one hour or more.[43] It is also given by infusion, e.g., 50 mg diluted to 500 ml and the infusion rate titrated against response.

Dopamine

Dopamine is one of the naturally occurring catecholamines.[22] It is the immediate metabolic precursor of noradrenaline. It has a very short half-life (less than two minutes) and is therefore given by infusion. Its effects are dose-dependent. At low doses of 2 to 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ its main effect is to bind to D_1 dopaminergic receptors which are present in the vessels of the splanchnic and coronary circulations, leading to vasodilatation. As the dose is increased (5 to 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$), it stimulates β_1 adrenergic receptors, producing positive inotropic and chronotropic effects on the heart. At higher doses (>20 $\mu g \cdot kg^{-1} \cdot min^{-1}$), it stimulates α_1 adrenergic receptors, producing vasoconstriction.[22]

Dobutamine

Dobutamine is similar in structure to dopamine, but has a bulky aromatic substituent on the amino group.[22] It was originally thought that dobutamine was a relatively selective β_1 agonist but it now seems that its pharmacological effects are more complex. Dobutamine exists in two enantiomeric forms, and the racemic mixture constitutes the compound used in clinical practice. Both enantiomers have actions at both α- and β-receptors. The (−)-isomer of dobutamine is a potent agonist at α_1-receptors, and can therefore produce marked vasoconstrictor responses. The (+)-isomer, however, is a potent α_1-receptor antagonist, and therefore it blocks the pressor effect of the (−)-isomer. The effects of both isomers at β-receptors is that of a full agonist, but the (+)-isomer is about ten times more potent than the (−)-isomer. Dobutamine may have greater selectivity for β_1 than for β_2 receptors.[22]

Dobutamine has a relatively greater inotropic than chronotropic effect on the heart. Its effects on peripheral resistance depends on the balance of effects of the α_1-mediated constrictor and β_1-mediated dilator actions. Overall there is little change. The drug has a half-life of about two minutes and must therefore be given by

infusion. The dose required is titrated against the desired response and will usually fall in the range of 2.5 to 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$.[22]

Which vasopressor?

Regional anaesthesia for obstetric practice differs from that in other surgical fields in that the needs of the fetus and placenta must be taken into consideration. Therefore the use of vasopressors in the obstetric patient will be discussed after discussing their use in other patients receiving a spinal or epidural block.

Non-obstetric use

From the above review of the pharmacology, it would seem that ephedrine has demonstrated its usefulness as a vasopressor agent for general use. It possesses both α- and β-receptor stimulating properties, and is therefore capable of increasing cardiac output and of increasing peripheral resistance. Many studies have demonstrated that ephedrine is a very effective vasopressor agent in this situation.[3,28,33,46-49] However, ephedrine is not without problems. It is a cerebral stimulant, it can increase myocardial irritability, produce a marked tachycardia and it is not a consistent vasoconstrictor. It is also common for tolerance to its effects to develop quickly, as it has at least a partial indirect action by releasing catecholamines from adrenergic nerve terminals.[43] It is also capable of producing post-block hypertension. It has also been reported to increase the plasma concentration of the local anaesthetic, which may be sufficient to produce local anaesthetic systemic toxicity during epidural anaesthesia.[50]

Methoxamine has proved to be a very effective vasopressor in non-obstetric practice.[35,36] As a pure directly acting α-agonist it consistently produces vasoconstriction. It does not increase myocardial irritability and has no cerebral stimulant effects. Tolerance is not a problem. It has been shown to decrease heart rate while slightly increasing stroke volume, the overall effects being an increase in blood pressure and a marked decrease in cardiac output.[46,51]

Phenylephrine is a pure α-agonist and therefore should have a profile of action which is essentially identical to that of methoxamine. There appear to be no studies on its use as a vasopressor in non-obstetric spinal or epidural anaesthesia. There also appears to be no work on the use of metaraminol or adrenaline in non-obstetric practice. Both drugs possess a good spectrum of actions and should therefore be quite suitable, although adrenaline is a cerebral stimulant. Dopamine at an infusion rate of 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ decreases systemic vascular resistance with little change in mean arterial pressure, but at doses of 4 and 8 $\mu g \cdot kg^{-1} \cdot min^{-1}$ will produce vasoconstriction with an increase in mean arterial pressure.[52] All three doses produce a dose-related increase in cardiac output, heart rate, central venous pressure and pulmonary capillary wedge pressure: this may be excessive at $8 \mu g \cdot kg^{-1} \cdot min^{-1}$.

Obstetric use

In obstetric practice it is important that hypotension is treated rapidly. It is well established that maternal hypotension leads to neonatal acidaemia, and this occurs more readily during spinal anaesthesia than during epidural anaesthesia.[53] Providing hypotension is avoided, regional anaesthesia does not adversely affect uterine blood flow.[54]

Ephedrine has proved very useful in managing spinal/epidural hypotension in obstetric practice, where it does not appear to affect uterine blood flow adversely[38,55-57] or to produce fetal asphyxia.[55,56,58,59] However, the problem of post-block hypertension is more likely to occur in obstetric practice[60] if it is given as a large "bolus" dose by *im* injection and oxytocic drugs are given postpartum.[32] Also, it may not correct fetal lactic acidosis despite adequate correction of hypotension.[61]

The use of methoxamine in obstetrics has been condemned as several animal studies have demonstrated that, while it increases maternal blood pressure, it causes a marked decrease in uterine blood flow, leading to fetal asphyxia.[56,62,63] However, two of these studies did not measure changes in maternal blood pressure or uterine blood flow during spinal hypotension[56,63]: the other study involved maintaining spinal hypotension for 45 min before the administration of methoxamine, with evidence fetal asphyxia was present even before administration.[62] Short periods (<two minutes) of maternal hypotension do not appear to harm the fetus[64,65] but, beyond this, fetal deterioration can develop. A more recent study[66] confirms that hypotension itself is most important to avoid, and that the vasopressor agent used to correct it does not, in itself, matter. Of greater relevance is the uterine response to methoxamine: it is a potent myometrial stimulant. Studies have shown a marked tendency to produce uterine hypertonia and even uterine tetany, which may result in fetal distress.[67,68] Of greater concern is the interaction between oxytocic drugs and methoxamine, which may result in severe postpartum hypertension[69] and has resulted in cerebral haemorrhage.[51] Caution must therefore be used if methoxamine is to be used in the obstetric patient.

Several obstetric studies confirm the ability of phenylephrine to produce an increase in blood pressure by vasoconstriction,[38] accompanied by bradycardia and a slight decrease in cardiac output. However, while some studies show that it does produce uterine vasoconstric-

tion,[70] others fail to show a decrease in uterine blood flow.[37] More recent work suggests that phenylephrine is safe as an obstetric vasopressor. There is no evidence of adverse maternal or fetal effects,[71] although care should be taken with the dose to avoid severe hypertension.[45] In view of the very similar pharmacological profile to methoxamine, one should similarly exercise great caution in the present dearth of research on phenylephrine in this role.

Dopamine is effective in restoring systemic blood pressure but reduces uterine blood flow.[72] It therefore cannot be recommended for obstetric use.

Metaraminol has been shown to restore maternal blood pressure but it frequently reduces uterine blood flow.[39,63] Adrenaline does not appear to have been studied in clinical practice in this situation. It would be expected to possess a similar spectrum of action to ephedrine, acting predominantly via β-receptors, but it also causes uterine vasoconstriction as a result of α-receptor stimulation.[31] It also has to be given by infusion and is a potent cerebral stimulant. It cannot therefore be recommended as a first-line agent.

How should the vasopressor be administered?

Most of the work concerning different methods of vasopressor administration has been conducted using ephedrine. Ephedrine can be administered effectively by *sc*, *im* or *iv* injection. In the presence of hypotension, absorption from *sc* or *im* injection sites may be unreliable and these routes should be reserved for prophylactic administration. Whether the routine prophylactic use of ephedrine is justified is open to discussion.[60] While *im* prophylaxis may be effective[73] in preventing hypotension, it immediately rules out any possibility of dose titration. This may lead to either inadequate treatment requiring further administration or, more seriously, hypertension,[60] which may be severe. This is particularly worrying in obstetric practice if the spinal block cannot be performed or is inadequate, requiring general anaesthesia[74]: neonatal acidaemia may result and hypertension may be severe with harmful consequences. This approach is not recommended. Subcutaneous administration has also been shown to be effective,[75] but the same reservations as for *im* use also apply. Intravenous administration appears to be the optimal route, and it seems that in the obstetric patient, at least, there is much to be gained from preventing hypotension in terms of maternal well-being[76] and neonatal acid-base status.[76,77] This appears to be better achieved by the use of an ephedrine infusion immediately after siting the spinal block.[77] The use of a prophylactic infusion of ephedrine may be useful in non-obstetric practice when a large fluid load may be undesirable,[78] but this needs further investigation.

Alternative and future management strategies

It seems that none of the currently available regimens is suitable as a single treatment. Combination therapy (e.g., fluid load and vasopressor) currently provides the best overall management strategy. Is there any prospect of a single therapy becoming available? It seems unlikely. Are there any drugs currently on the market which may have a role to play? Possibly. Ketamine, a drug used for its anaesthetic and analgesic properties, has sympathomimetic actions and may be helpful in preventing hypotension,[79] although reservations must be expressed because of the well-known hallucinatory side effects of ketamine. Its anaesthetic properties also make it unsuitable for obstetric use.

Phosphodiesterase inhibitors (e.g., enoximone, milrinone) are members of a new class of drugs introduced in recent years for the management of heart failure, where their effect is to increase cardiac output while decreasing peripheral resistance. Milrinone can cause an increase in uterine blood flow,[80] but simultaneously reduces blood pressure. As a sole agent this is of little value, but may be beneficial in combination with a vasoconstrictor agent which would otherwise reduce placental perfusion and this requires investigation.

Dopexamine is a relatively new inotropic drug with actions on dopaminergic and β_2-adrenergic receptors. It appears to have no vasoconstrictor properties. As yet there are no reports of its use in treating spinal/epidural hypotension. Its actions are to increase cardiac output while producing splanchnic vasodilation. It may have a place in treating spinal/epidural hypotension by its inotropic actions without producing vasoconstriction, and this spectrum of activity may prove very useful in the obstetric patient.

Conclusions

No single management strategy is effective in treating hypotension produced by spinal and epidural anaesthesia. Vasopressor agents continue to be of value in managing this condition. Ephedrine has proved useful in non-obstetric practice but it is not always reliable. A drug with a greater peripheral vasoconstrictor action may be more appropriate in many circumstances. Either methoxamine or phenylephrine would seem to fill this role adequately.

It seems that ephedrine is clearly the agent of choice in obstetric practice, particularly if used as a prophylactic infusion, but it must be borne in mind that a pure vasoconstrictor agent may be cautiously used to good effect instead of, or in addition to, ephedrine. Phenylephrine seems to be the agent used most frequently in this role, and further research may define its position more clearly.

References

1 *Wildsmith JAW.* The history and development of local anaesthesia. *In:* Wildsmith JAW, Armitage EN (Eds.). Principles and Practice of Regional Anaesthesia, Edinburgh: Churchill Livingstone, 1987: 1–7.

2 *Kestin IG.* Spinal anaesthesia in obstetrics. Br J Anaesth 1991; 66: 596–607.

3 *Greene NM, Brull SJ.* Physiology of Spinal Anesthesia, 4th ed. Baltimore: Williams & Wilkins. 1993: 85–199, 309–43, and 357–80.

4 *Robson S, Hunter S, Boys R, Dunlop W, Bryson M.* Changes in cardiac output during epidural anaesthesia for Caesarean section. Anaesthesia 1989; 44: 475–9.

5 *Baron J-F, Coriat P, Mundler O, Fauchet M, Bousseau D, Viars P.* Left ventricular global and regional function during lumbar epidural anesthesia in patients with and without angina pectoris. Influence of volume loading. Anesthesiology 1987; 66: 621–7.

6 *Hahn RG.* Blood volume at the onset of hypotension during TURP performed under epidural anaesthesia. Eur J Anaesthesiol 1993; 10: 219–25.

7 *Hahn RG.* Increased haemodilution in hypotension induced by epidural anaesthesia. Acta Anaesthesiol Scand 1993; 37: 357–60.

8 *Gajraj NM, Victory RA, Pace NA, Van Elstraete AC, Wallace DH.* Comparison of an ephedrine infusion with crystalloid administration for prevention of hypotension during spinal anesthesia. Anesth Analg 1993; 76: 1023–6.

9 *Rout CC, Rocke DS, Levin J, Gouws E, Reddy D.* A reevaluation of the role of crystalloid preload in the prevention of hypotension associated with spinal anaesthesia for elective cesarean section. Anesthesiology 1993; 79: 262–9.

10 *Wennberg E, Frid I, Haljamäe H, Norén H.* Colloid (3% dextran 70) with or without ephedrine infusion for cardiovascular stability during extradural Caesarean section. Br J Anaesth 1992; 69: 13–8.

11 *Stanton-Hicks M d'A.* Cardiovascular effects of extradural anaesthesia. Br J Anaesth 1975; 47: 253–63.

12 *Shimosato S, Etsten BE.* The role of the venous system in cardiocirculatory dynamics during spinal and epidural anesthesia in man. Anesthesiology 1969; 30: 619–28.

13 *Sancetto SM, Lynn RB, Simeone FA, Scott RW.* Studies of the hemodynamic changes in humans following induction of low and high spinal anesthesia. 1. General considerations of the problem. The changes in cardiac output, brachial arterial pressure, peripheral and pulmonary oxygen contents and peripheral blood flows induced by spinal anesthesia in humans not undergoing surgery. Circulation 1952; 6: 559–71.

14 *Milwidsky H, de Vries A.* Regulation of blood pressure during spinal anesthesia: observations on intramuscular pressure and skin temperature. Anesthesiology 1948; 9: 258–75.

15 *Blake DW, Donnan G, Novella J, Hackman C.* Cardiovascular effects of sedative infusions of propofol and midazolam after spinal anaesthesia. Anaesth Intensive Care 1988; 16: 292–8.

16 *Otton PE, Wilson EJ.* The cardiocirculatory effects of upper thoracic epidural analgesia. Can Anaesth Soc J 1966; 13: 541–9.

17 *McLean APH, Mulligan GW, Otton P, MacLean LD.* Hemodynamic alterations associated with epidural anesthesia. Surgery 1967; 62: 79–87.

18 *Giasi RM, D'Agostino, Covino BG.* Absorption of lidocaine following subarachnoid and epidural administration. Anesth Analg 1979; 58: 360–3.

19 *Greene NM.* Blood levels of local anesthetics during spinal and epidural anesthesia (Editorial). Anesth Analg 1979; 58: 357–9.

20 *Harrison DC, Sprouse JH, Morrow AG.* The antiarrhythmic properties of lidocaine and procaine amide: clinical and physiological studies of their cardiovascular effects in man. Circulation 1963; 28: 486–91.

21 *Jorfeldt L, Löfström B, Pernow B, Wahren J, Widman B.* The effect of local anaesthetics on the central circulation and respiration in man and dog. Acta Anaesthesiol Scand 1968; 12: 153–69.

22 *Hoffman BB, Lefkowitz RJ.* Catecholamines and sympathomimetic drugs. *In:* Goodman Gilman A, Rall TW, Nies AS, Taylor P (Eds.). The Pharmacological Basis of Therapeutics 8th ed., New York: Pergamon Press. 1990: 187–220.

23 *Salvesky FC, Whalley DG, Kalant D, Crawhall J.* Epidural epinephrine and the systemic circulation during peripheral vascular surgery. Can J Anaesth 1990; 37: 160–5.

24 *Stanton-Hicks M, Berges PU, Bonica JJ.* Circulatory effects of peridural block: IV. Comparison of the effects of epinephrine and phenylephrine. Anesthesiology 1973; 39: 308–14.

25 *Kleinerman J, Sancetta SM, Hackel DB.* Effects of high spinal anesthesia on cerebral circulation and metabolism in man. J Clin Invest 1958; 37: 285–93.

26 *Dohi S, Naito H, Takahashi T.* Age-related changes in blood pressure and duration of motor block in spinal anesthesia. Anesthesiology 1979; 50: 319–23.

27 *Graves CL, Klein RL.* Central venous pressure monitoring during routine spinal anaesthesia. Arch Surg 1968; 97: 843–7.

28 *Hemmingsen C, Poulsen JA, Risbo A.* Prophylactic ephedrine during spinal anaesthesia: double-blind study in patients in ASA groups I-III. Br J Anaesth 1989; 63: 340–2.

29 *Kennedy WF Jr, Bonica JJ, Akamatsu TJ, Ward RJ, Martin WE, Grinstein A.* Cardiovascular and respiratory effects of subarachnoid block in the presence of acute blood loss. Anesthesiology 1968; 29: 29–35.

30 *Bonica JJ, Kennedy WF Jr, Akamatsu TJ, Gerbershagen HU.* Circulatory effects of peridural block: III. Effects of acute blood loss. Anesthesiology 1972; 36: 219–27.
31 *Greiss FC.* The uterine vascular bed: effect of adrenergic stimulation. Obstet Gynecol. 1963; 21: 295–301.
32 *Levinson G, Shnider SM.* Vasopressors in obstetrics. Clinical Anesthesiology 1974; 10: 77–109.
33 *Ockerblad NF, Dillon TG.* The use of ephedrine in spinal anesthesia. JAMA 1927; 88: 1135–6.
34 *Dripps RD, Deming MV.* An evaluation of certain drugs used to maintain blood pressure during spinal anesthesia; comparison of ephedrine, paredine, pitressin-ephedrine and methedrine in 2500 cases. Surg Gynecol Obstet 1946; 83: 312–22.
35 *King BD, Dripps RD.* The use of methoxamine for maintenance of the circulation during spinal anesthesia. Surg Gynecol Obstet 1950; 90: 659–65.
36 *Poe MF.* Use of methoxamine hydrochloride as a pressor agent during spinal anesthesia. Anesthesiology 1952; 13: 89–93.
37 *Greiss FC Jr., Crandell DL.* Therapy for hypotension induced by spinal anesthesia during pregnancy. JAMA 1965; 191: 793–6.
38 *Labartino L, Mojdehi E, Mauro AL.* Management of hypotension following spinal anesthesia for cesarean section. Anesth Analg 1966; 45: 179–82.
39 *James FM III, Greiss FC Jr, Kemp RA.* An evaluation of vasopressor therapy for maternal hypotension during spinal anesthesia. Anesthesiology 1970; 33: 25–34.
40 *Cabalum T, Zugaib M, Lieb S, Nuwayhid B, Brinkman CR III, Assali NS.* Effects of dopamine on hypotension induced by spinal anesthesia. Am J Obstet Gynecol 1979; 133: 630–4.
41 *Clark RB, Brunner JA III.* Dopamine for the treatment of spinal hypotension during cesarean section. Anesthesiology 1980; 53: 514–7.
42 *Takasaki M.* Cardiovascular support drugs during thoracic epidural analgesia (Letter). Anesthesiology 1988; 68: 175.
43 *Vickers MD, Morgan M, Spencer PSJ.* Drugs in Anaesthetic Practice, 7th ed. Oxford: Butterworth-Heinemann Ltd. 1991: 301–53.
44 *Reynolds JRF (Ed.).* Martindale: The Extra Pharmacopoeia, 30th ed. London: The Pharmaceutical Press. 1993: 1244–8.
45 *Taylor JC, Tunstall ME.* Dosage of phenylephrine in spinal anaesthesia for Caesarean section (Letter). Anaesthesia 1991; 46: 314–5.
46 *Ward RJ, Kennedy WF Jr, Bonica JJ, Martin WE, Tolas AG, Akamatsu T.* Experimental evaluation of atropine and vasopressors for the treatment of hypotension of high subarachnoid anesthesia. Anesth Analg 1966; 45: 621–9.
47 *Thornburn J.* Subarachnoid blockade and total hip replacement. Effect of ephedrine on intraoperative blood loss. Br J Anaesth 1985; 57: 290–3.
48 *Butterworth JF IV, Piccione W Jr, Berrizbeitia LD, Dance G, Shemin RJ, Cohn LH.* Augmentation of venous return of adrenergic agonists during spinal anesthesia. Anesth Analg 1986; 65: 612–6.
49 *Engberg G, Wiklund L.* The circulatory effects of intravenously administered ephedrine during epidural blockade. Acta Anaesthesiol Scand, 1978 Suppl; 66: 27–36.
50 *Mather LE, Tucker GT, Murphy TM, Stanton-Hicks M d'A, Bonica JJ.* Hemodynamic drug interaction: peridural lidocaine and intravenous ephedrine. Acta Anaesthesiol Scand 1976; 20: 207–10.
51 *Smith NT, Corbascio AN.* The use and misuse of pressor agents. Anesthesiology 1970; 33: 58–101.
52 *Lundberg J, Norgren L, Thomson D, Werner O.* Hemodynamic effects of dopamine during thoracic epidural analgesia in man. Anesthesiology 1987; 66: 641–6.
53 *Ratcliffe FM, Evans JM.* Neonatal wellbeing after elective caesarean delivery with general, spinal, and epidural anaesthesia. Eur J Anaesthesiol 1993; 10: 175–81.
54 *Veille JC, Youngstrom P, Kanaan C, Wilson B.* Human umbilical artery flow velocity waveforms before and after regional anesthesia for cesarean section. Obstet Gynecol 1988; 72: 890–3.
55 *Shnider SM, deLorimier AA, Holl JW, Chapler FK, Morishima HO.* Vasopressors in obstetrics. I. Correction of fetal acidosis with ephedrine during spinal hypotension. Am J Obstet Gynecol 1968; 102: 911–9.
56 *Eng M, Berges PU, Ueland K, Bonica JJ, Parer JT.* The effects of methoxamine and ephedrine in normotensive pregnant primates. Anesthesiology 1971; 35: 354–60.
57 *Hollmén AI, Jouppila R, Albright GA, Jouppila P, Vierola H, Koivula A.* Intervillous blood flow during Caesarean section with prophylactic ephedrine and epidural anaesthesia. Acta Anaesthesiol Scand 1984; 28: 396–400.
58 *Wright RG, Shnider SM, Levinson G, Rolbin SH, Parer JT.* The effect of maternal administration of ephedrine on fetal heart rate and variability. Obstet Gynecol 1981; 57: 734–8.
59 *Brizgys RV, Dailey PA, Shnider SM, Kotelko DM, Levinson G.* The incidence and neonatal effects of maternal hypotension during epidural anesthesia for cesarean section. Anesthesiology 1987; 67: 782–6.
60 *Rolbin SH, Cole AFD, Hew EM, Pollard A, Virgint S.* Prophylactic intramuscular ephedrine before epidural anaesthesia for Caesarean section: efficacy and actions on the foetus and newborn. Can Anaesth Soc J 1982; 29: 148–53.
61 *Antoine C, Young BK.* Fetal lactic acidosis with epidural anesthesia. Am J Obstet Gynecol 1982; 142: 55–9.
62 *Schnider SM, deLorimier AA, Asling JH, Morishima JH.* Vasopressors in obstetrics. II. Fetal hazards of methoxamine

administration during obstetric anesthesia. Am J Obstet Gynecol 1970; 106: 680–6.

63 *Ralston DH, Shnider SM, deLorimier AA.* Effects of equipotent ephedrine, metaraminol, mephentermine, and methoxamine on uterine blood flow in the pregnant ewe. Anesthesiology 1974; 40: 354–70.

64 *Corke BC, Datta S, Ostheimer GW, Weiss JB, Alper MH.* Spinal anaesthesia for Caesarean section. The influence of hypotension on neonatal outcome. Anaesthesia 1982; 37: 658–62.

65 *Ebner H, Barcohana J, Bartoshuk AK.* Influence of post-spinal hypotension on the fetal electrocardiogram. Am J Obstet Gynecol 1960; 80: 569–72.

66 *Wright PMC, Iftikhar M, Fitzpatrick KT, Moore J, Thompson W.* Vasopressor therapy for hypotension during epidural anesthesia for caesarean section: effects on maternal and fetal flow velocity ratios. Anesth Analg 1992; 75: 56–63.

67 *Vasicka A, Hutchinson HT, Eng M, Allen CR.* Spinal and epidural anesthesia, fetal and uterine response to acute hypo- and hypertension. Am J Obstet Gynecol 1964; 90: 800–10.

68 *Senties LG, Arrelano G, Casellas F, Ontiveros E, Santos J.* Effects of some vasopressor drugs upon uterine contractility in pregnant women. Am J Obstet Gynecol 1970; 107: 892–7.

69 *Casady GN, Moore DC, Bridenbaugh LD.* Postpartum hypertension after the use of vasoconstrictor and oxytocic drugs. JAMA 1960; 172: 1011–5.

70 *Greiss FC Jr., Van Wilkes D.* Effects of sympathomimetic drugs and angiotensin on the uterine vascular bed. Obstet Gynecol 1964; 23: 925–30.

71 *Ramanathan S, Grant GJ.* Vasopressor therapy for hypotension due to epidural anesthesia for cesarean section. Acta Anaesthesiol Scand 1988; 32: 559–65.

72 *Rolbin SH, Levinson G, Shnider SM, Biehl DR, Wright RG.* Dopamine treatment of spinal hypotension decreases uterine blood flow in the pregnant ewe. Anesthesiology 1979; 51: 36–40.

73 *Gutsche BB.* Prophylactic ephedrine preceding spinal analgesia for cesarean section. Anesthesiology 1976; 45: 462–5.

74 *Rout CC, Rocke DA, Brijball R, Koovarjee RV.* Prophylactic intramuscular ephedrine prior to Caesarean section. Anaesth Intensive Care 1992; 20: 448–52.

75 *Engberg G, Wiklund L.* The use of ephedrine for prevention of arterial hypotension during epidural blockade. A study of the central circulation after subcutaneous premedication. Acta Anesthesiol Scand 1978 Suppl; 66: 1–26.

76 *Datta S, Alper MH, Ostheimer GW, Weiss JB.* Method of ephedrine administration and nausea and hypotension during spinal anesthesia for cesarean section. Anesthesiology 1982; 56: 68–70.

77 *Kang YG, Abouleish E, Caritis S.* Prophylactic intravenous ephedrine infusion during spinal anesthesia for cesarean section. Anesth Analg 1982; 61: 839–42.

78 *Frazer RS, Edwards GM.* Prophylactic ephedrine infusion in obstetric anaesthesia (Letter). Br J Anaesth 1990; 64: 651.

79 *Hemmingsen C, Neilsen JEK.* Intravenous ketamine for prevention of severe hypotension during spinal anaesthesia. Acta Anaesthesiol Scand 1991; 35: 755–7.

80 *Santos AC, Baumann AL, Wlody D, Pedersen H, Morishima HO, Finster M.* The maternal and fetal effects of milrinone and dopamine in normotensive pregnant ewes. Am J Obstet Gynecol 1992; 166: 257–62.