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The Use of Ephedrine in Epidural Analgesia

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ABSTRACT

The changes in arterial blood pressure following high epidural blockade with bupivacaine adrenaline, etidocaine adrenaline and HS 37 adrenaline have been retrospectively evaluated from a clinical study in middle-aged and elderly patients, with special emphasis on the role of ephedrine premedication. Epidural blockade without the use of vasopressors was usually followed by hypotension, but after ephedrine premedication the changes in blood pressure were insignificant. The heart rate did not change more in groups with ephedrine than in those without ephedrine premedication, although the incidence of bradycardia was lower with ephedrine premedication. No side effects of ephedrine were noted.

INTRODUCTION

High epidural as well as subarachnoidal analgesia are often followed by arterial hypotension. It is considered that the primary cause is a blockade of a great part of the sympathetic nervous system with ensuing vasodilatation in the anaesthetized area (4, 5, 11). If the blockade reaches the upper four thoracic segments, cardiac sympathetic nerves are involved and cardiac output may be lowered (7, 11, 22, 23, 24). Even in lower epidural blockade the compensatory vasoconstriction in the part of the body not affected is often insufficient to prevent hypotension, especially in elderly patients and patients with cardiac and vascular diseases (5). Hypotension is the most common complication in epidural and spinal analgesia (5, 18, 19). The magnitude of the decrease in blood pressure is as great during epidural as during spinal analgesia (4, 6, 11, 26), but the onset is slower during epidural analgesia. In spinal analgesia pressor agents are usually given prophylactically, but in epidural analgesia with a slower change in peripheral and central circulation, vagal blockade by atropine in addition to volume substitution have been regarded as sufficient to prevent hypotension (9). Despite this treatment the decrease in arterial blood pressure is pronounced in many patients calling for further therapy (15).

The results of several studies (20, 21, 27) indicate that ephedrine is a suitable drug to prevent hypotension in spinal analgesia. Ephedrine has also often been used as a pressor agent in epidural analgesia (3, 9, 10). However, haemodynamic studies of the effect of ephedrine in epidural analgesia are lacking. Ephedrine is a sympathomimetic amine with both central cardiostimulatory and peripheral vasomotor action, resulting in either vasoconstriction or vasodilatation (1, 12, 27). The cardiovascular effect is similar to that of adrenaline and the vasoconstrictive effect to that of noradrenaline, but both are less pronounced and more long-acting (2, 14).

During a clinical trial of some new long-acting anaesthetic drugs in epidural analgesia, it was necessary to use ephedrine to avoid serious hypotension (15). In the first part of the study atropine and volume substitution were used to prevent hypotension, but during the investigation it became obvious that in spite of this treatment there was a considerable decrease in blood pressure. The second part of the study was therefore performed after prophylactic administration of ephedrine. This is a retrospective study of the material and an attempt to evaluate the effect of ephedrine on the arterial blood pressure and heart rate.

PATIENTS

From the above mentioned study all patients aged 40 to 71 years with a preanalgesic systolic blood pressure of 100 to 160 mmHg were selected, and the changes in arterial blood pressure and pulse rate studied. 133 patients were included, of whom 74 were premedicated with ephedrine. For the epidural blockade bupivacaine 0.5% adrenaline, HS 37 0.75% or 1% adrenaline and etidocaine 0.75%, 1% or 1.5% adrenaline were used. All solutions contained adrenaline 1 : 200 000=5 μg/ml. The distribution of the patients given the various local anaesthetic agents is pre-

Table I. *Distribution of patients. Number, age, preanalgesic systolic blood pressure (SBP) and heart rate (HR). The values are presented as means* ±S.D.

	No. of patients	Age (y.)	SBP (mmHg)	HR (beats · min^{-1})
Without ephedrine				
Bupivacaine 0.5% adrenaline	13	58.1±8.9	141±13.7	80±23.7
HS 37 0.75% adrenaline	14	56.0±8.1	124±12.7	76±10.8
HS 37 1% adrenaline	18	57.8±8.8	137±17.7	84±16.6
Etidocaine 0.75% adrenaline	14	54.4±6.2	134±17.7	75±16.1
With ephedrine				
Bupivacaine 0.5% adrenaline	18	60.2±8.9	125±14.0	75±13.8
HS 37 1% adrenaline	19	54.4±9.1	133±13.7	75±13.6
Etidocaine 1% adrenaline	23	55.6±6.7	138±15.8	79±12.8
Etidocaine 1.5% adrenaline	14	53.7±8.3	127±10.1	77±12.3

sented in Table I. Epidural blockade with bupivacaine 0.5% adrenaline and HS 37 1% adrenaline included patients both with and without ephedrine premedication. For the epidural blockade with etidocaine adrenaline, the lower concentration of 0.75% was used in the patients not premedicated with ephedrine, and the higher concentrations of 1% and 1.5% in the ephedrine-premedicated patients.

METHODS

The patients not receiving ephedrine were sedated one hour before analgesia with 10 mg of diazepam or 50 mg pethidine, given subcutaneously together with atropine 0.5 mg. In the patients receiving ephedrine, 10 mg of morphine and 4 mg scopolamine were used for sedation. Before the epidural induction 50 mg of ephedrine and 10 mg of lidocaine were injected subcutaneously in the lumbar region, and also served as an anaesthetic for the puncture with the epidural needle, which was usually made between the third and fourth lumbar vertebrae. The local anaesthetic agent was injected directly through the needle about five min after the ephedrine premedication. A total volume of 20 ml was given divided between the test dose of 3 ml and the main dose of 17 ml injected 1 to 2 min later. In all patients intravenous infusion of 500 ml of 10% invertose solution (Inverdex Special 10%®) was begun immediately before the epidural injection and given in the course of 15 min. Blood pressure below 90 mmHg was primarily treated with 500 ml of dextran 70 6% (Macrodex®), and more profound hypotension below 70 mmHg in addition to volume expansion with ephedrine 10 mg intravenously. Heart rate below 50/min was treated with atropine 0.5 mg as a single dose intravenously.

The anaesthetic level was estimated by pin-prick. E.c.g. was supervised in all patients with a cardioscope. Systolic and diastolic blood pressure and heart rate were measured from the brachial or radial arteries by auscultation or palpation every five minutes after the epidural injection, and the changes during one hour were noted. The mean arterial blood pressure (MABP) was calculated according to the formula

$$MABP = DBP + \frac{SBP - DBP}{3},$$

where SBP=systolic arterial blood pressure and DBP=diastolic arterial blood pressure. The blood pressure and heart rate recorded in the anaesthetic room after sedation but before analgesia were used as control values=100%. The statistical calculations were made according to Student's *t*-test for unpaired data. $P<0.05$ was considered significant.

RESULTS

Systolic blood pressure related to the anaesthetic level

HS 37 0.75% adrenaline gave less spread of analgesia and significantly ($P<0.001$) less decrease in systolic blood pressure than did epidural blockade with any of the other agents. Hence, HS 37 0.75% adrenaline was not considered comparable with the other agents and will not be considered further. The analgesia reached an upper limit of T_5 or above in 87% of the patients not receiving ephedrine, and in

Table II. *Distribution of patients as regards the upper segmental spread of analgesia.*

	T_{10}–T_6	T_5–T_3	T_2–C_6
Without ephedrine			
Bupivacaine 0.5% adrenaline	2	5	6
HS 37 0.75% adrenaline	5	9	–
HS 37 1% adrenaline	1	13	4
Etidocaine 0.75% adrenaline	3	8	3
With ephedrine			
Bupivacaine 0.5% adrenaline	4	8	6
HS 37 1% adrenaline	2	12	5
Etidocaine 1% adrenaline	1	11	11
Etidocaine 1.5% adrenaline	1	7	6

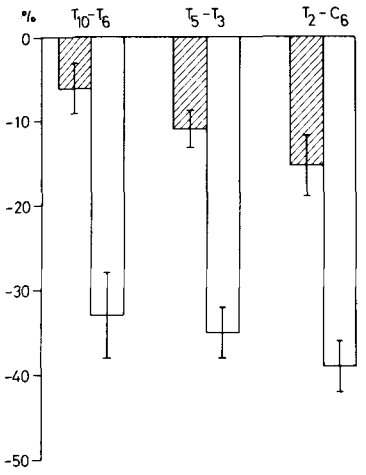

Fig. 1. The maximum decrease of systolic blood pressure related to the upper analgesic limit in the patients with (▨) and without (□) ephedrine premedication (mean±S.E.).

89% of those receiving ephedrine premedication (Table II). If all patients *without ephedrine* premedication were considered the maximum decrease in systolic blood pressure following epidural blockade with an analgesic limit of T_{10} to T_6 was 33±14% against 39±10% for those with an analgesic spread between T_2 and C_6 (Fig. 1). *With ephedrine* premedication the decrease in systolic blood pressure at the same levels was 6±9% and 15±19%, respectively. The change in systolic blood pressure at the different limits of analgesia did not differ significantly within the group with or the group without ephedrine premedication, but there was a significant difference between the groups receiving and not receiving this premedication (analgesic limit T_{10} to T_6, $P<0.05$; analgesic limit T_5 to T_3, $P<0.001$; analgesic limit T_2 to C_6, $P<0.01$; Fig. 1).

Changes in systolic blood pressure in relation to time after injection

Without ephedrine premedication there was already a significant fall in systolic blood pressure in all groups 5 min after the injection of the main dose in the epidural space ($P<0.05$). The lowest values were reached after 15 to 30 min, after which the blood pressure remained considerably reduced during the investigation period of one hour (Fig. 2). The decrease did not at any point of time significantly differ between bupivacaine 0.5% adrenaline, HS 37 1% adrenaline, and etidocaine 0.75% adrenaline, the maximum decrease with the three agents being 32%, 27% and 21%, respectively. *With ephedrine* the changes in systolic blood pressure were small, the mean values varying between ±6% in all groups, and there were no significant differences between the various local anaesthetic drugs at any time. The difference between the patients receiving and those not receiving ephedrine premedication was already significant after 5 min ($P<0.05$ to $P<0.001$).

Changes in diastolic and mean arterial blood pressure in relation to time after epidural injection

In a previous study (15) bupivacaine 0.5% adrenaline, HS 37 1% adrenaline and etidocaine 0.75% and 1% adrenaline were found to have the same anaesthetic spread, and as shown above, there were no significant differences between these groups as regards the influence on the systolic blood pressure. In 48 patients belonging to these groups, 25 with and 23 without ephedrine premedication, diastolic blood pressures were recorded before and after the epidural blockade, and from them the changes in diastolic and mean blood pressure could be analysed.

Without ephedrine the diastolic and the mean blood pressure decreased in a way similar to the systolic blood pressure (maximum decrease 22% and 19%, respectively). *With ephedrine* neither the diastolic nor the mean blood pressure changed significantly from the preanaesthetic value (maxi-

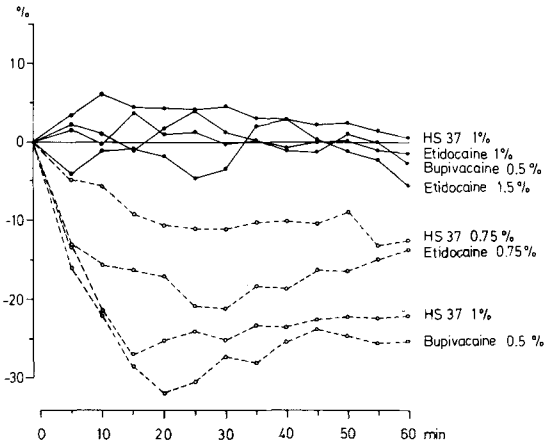

Fig. 2. Mean values of the relative change of systolic blood pressure related to the time after the epidural injection in the groups with (●—●) and without (○---○) ephedrine premedication. All agents contained adrenaline.

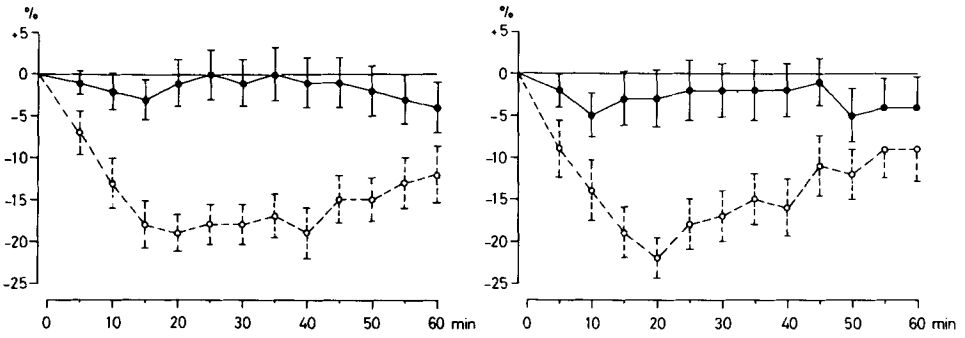

Fig. 3. Mean values of the relative change of mean (left) and diastolic (right) blodd pressure related to time after the epidural injection in patients with (●—●) and without (○---○) ephedrine premedication. (Mean values ±S.E.).

mum decrease 6% and 5%, respectively) (Fig. 3). There was a significant difference between the patients with and without ephedrine premedication from 5 min after the epidural injection as regards both diastolic and mean blood pressure ($P<0.05$ to $P<0.001$).

Maximum changes in systolic blood pressure

Without ephedrine premedication the mean maximum decrease in systolic blood pressure at any point during the first hour was about 35% of the preanalgesic value in all groups and *with ephedrine* premedication the mean maximum decrease varied in the groups between 8% and 17% (Table III). There was a significant difference between the groups with and without ephedrine premedication ($P<0.001$).

In absolute terms the systolic blood pressure decreased in all groups without ephedrine premedication to 90 mmHg or less in 70% and to 80 mmHg or less in approximately 50% of the patients (Table IV). With ephedrine premedication a blood pressure fall to 80 mmHg or less occurred only in the etidocaine groups.

If the highest measured systolic blood pressures were considered, there was *with ephedrine* premedication an average increase of 11 to 17%, while *without ephedrine* the mean values of the highest measured blood pressures were lower than the control values (−2% to −9%). The differences between the groups with and without ephedrine were significant ($P<0.001$). Without ephedrine the maximum recorded increase in systolic blood pressure was from 145 to 175 mmHg and with ephedrine from 155 to 220 mmHg.

Table III. *Maximum relative changes of systolic blood pressure and heart rate in per cent of the preanalgesic values (means* ±S.D.).

	Systolic blood pressure (SBP) Relative change (%) of		Heart rate (HR) Relative change (%) of	
	Lowest SBP	Highest SBP	Lowest HR	Highest HR
Without ephedrine				
Bupivacaine 0.5% adrenaline	−35.8±12.7	−8.5±11.3	0.6±17.7	28.3±19.6
HS 37 0.75% adrenaline	−18.4±18.4	5.0±11.2	0.9±18.9	34.4±21.9
HS 37 1% adrenaline	−36.7±11.1	−6.6±14.3	−6.7±11.9	21.6±18.7
Etidocaine 0.75% adrenaline	−34.5±14.2	−2.0±13.1	4.4±22.1	43.1±31.1
With ephedrine				
Bupivacaine 0.5% adrenaline	−10.7±13.8	12.5±11.8	−9.9±18.1	28.6±23.3
HS 37 1% adrenaline	−8.3±11.0	13.5±14.3	−0.3±18.4	41.5±26.8
Etidocaine 1% adrenaline	−11.1±16.2	11.3±14.7	−3.5±10.7	30.1±23.0
Etidocaine 1.5% adrenaline	−17.1±15.3	17.2±18.9	−14.5±15.7	22.7±23.4

Table IV. *Number of patients with hypotension in absolute and relative terms of the total number of patients in each group*

	Systolic blood pressure		
	<90 mmHg	<80 mmHg	<70 mmHg
Without ephedrine			
Bupivacaine 0.5% adrenaline	10/13 (71%)	6/13 (46%)	1/13 (8%)
HS 37 0.75% adrenaline	6/14 (43%)	3/14 (21%)	1/14 (7%)
HS 37 1% adrenaline	13/18 (72%)	8/18 (45%)	4/18 (22%)
Etidocaine 0.75% adrenaline	10/14 (71%)	8/14 (57%)	2/14 (14%)
With ephedrine			
Bupivacaine 0.5% adrenaline	4/18 (22%)		
HS 37 1% adrenaline	2/19 (11%)		
Etidocaine 1% adrenaline	3/23 (13%)	2/23 (9%)	1/23 (4%)
Etidocaine 1.5% adrenaline	6/14 (43%)	3/14 (22%)	1/14 (7%)

Changes in heart rate

Irrespective of ephedrine premedication, the heart rate tended to increase. The increase was more pronounced during the first 30 min in all groups, except in the group with etidocaine 1.5% adrenaline, where the maximum increase was not reached until after 45 min. If all patients *without ephedrine* premedication were considered, there was a greater increase in mean heart rate during the first 10 min on comparing with all patients *with ephedrine* premedication ($P<0.05$), but after this there was no difference (Fig. 4). Furthermore, there were no significant differences between the groups with and the groups without ephedrine premedication with regard to the maximum increase in heart rate (Table III).

Additional treatment of hypotension and bradycardia

In the patients not premedicated with ephedrine, dextran 70 (Macrodex®) was given to 31 out of 59 patients (52%), and in 7 of those ephedrine was given intravenously in addition. With ephedrine premedication dextran 70 was given to 8 out of 74 patients (10%) and two of the patients with etidocaine adrenaline 1.5% had additional intravenous ephedrine (Table V). Slow heart rate requiring therapy, mainly atropine intravenously, occurred more often in the patients not premedicated with ephedrine, 20 out of 59 (33%) compared with 14 out of 74 (18%) of the ephedrine-premedicated patients. The frequency of patients with bradycardia requiring atropine was higher in the etidocaine groups (Table V).

Side effects

No side effects of ephedrine such as palpitations, tachycardia or arrythmias were found in any of the patients. Nausea occurred rarely in patients with ephedrine premedication (6%), compared with those without ephedrine premedication (20%). Most of the patients who experienced nausea were

Table V. *Frequency of patients in each group with hypotension treated with dextran, atropine and ephedrine i.v.*

	Dextran 70 6%	Atropine 0.5 mg i.v.	Additional ephedrine 10 mg i.v.
Without ephedrine			
Bupivacaine 0.5% adrenaline	6/13 (46%)	5/13 (38%)	1/13 (8%)
HS 37 0.75% adrenaline	8/14 (57%)	4/14 (29%)	
HS 37 1% adrenaline	8/18 (45%)	4/18 (22%)	2/18 (11%)
Etidocaine 0.75% adrenaline	9/14 (64%)	7/14 (50%)	4/14 (29%)
With ephedrine			
Bupivacaine 0.5% adrenaline	2/18 (11%)	3/18 (17%)	
HS 37 1% adrenaline	1/19 (6%)	2/19 (11%)	
Etidocaine 1% adrenaline	4/23 (17%)	3/23 (13%)	
Etidocaine 1.5% adrenaline	1/14 (7%)	6/14 (43%)	2/14 (14%)

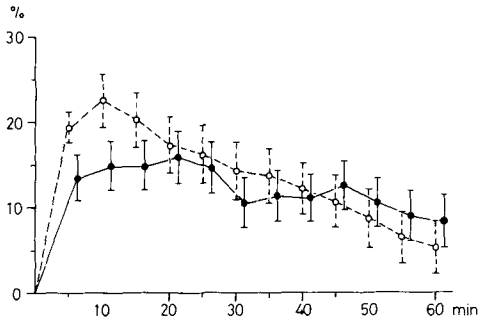

Fig. 4. Relative change in mean heart rate related to the time after the epidural injection in patients with (●—●) and without (O---O) ephedrine premedication. The values are presented as means ±S.E.

found in the etidocaine group without ephedrine premedication. The nausea was usually connected with a sudden drop in blood pressure.

DISCUSSION

Blood pressure changes in the patients not receiving ephedrine

Without prophylactic use of ephedrine, the high lumbar epidural blockade with local anaesthetics containing adrenaline caused hypotension of a considerable degree in these middle-aged and elderly patients. The maximum decrease did not occur until 15 to 30 min after the epidural injection, but the blood pressure was significantly decreased already 5 min after the epidural injection. Despite prophylactic treatment with atropine and volume expanders, the maximum decrease in systolic blood pressure, around 35%, was of the same magnitude as that reported in earlier studies of high spinal analgesia (13, 24). Additional treatment with dextran to 50% of the patients without ephedrine premedication did not prevent a fall in systolic blood pressure to 80 mmHg or less. A blood pressure of this level is usually regarded as acceptable, but could in elderly patients reduce the cerebral and myocardial blood flow to a critical level (5). The diastolic blood pressure and the mean arterial blood pressure were reduced in a way similar to the systolic blood pressure. As the filling of the coronary arteries mainly occurs during diastole (17), a marked fall in the diastolic blood pressure could be disasterous for the coronary circulation. Some patients without ephedrine premedication had symptoms of insufficient peripheral circulation with paleness or cyanosis and nausea in connection with the decrease in blood pressure. The symptoms disappeared when the blood pressure was restored to a normal level. It is important to note that the decrease in systolic blood pressure was nearly as great at relatively low epidural blockade, at T_6 or lower, as in high epidural blockade, T_2 or higher. In clinical practice, most lumbar epidural blockades must reach the level of T_6 to produce a satisfactory analgesia for surgery in the lower part of the abdomen and the legs, and thus may cause hypotension of considerable degree.

Bupivacaine 0.5% adrenaline, HS 37 1% adrenaline and etidocaine 1% adrenaline were in a previous study (15) estimated to have the same analgesic effect, and two of them, bupivacaine 0.5% adrenaline and HS 37 1% adrenaline, also produced an equal degree of hypotension. The incidence of a sudden fall in systolic blood pressure connected with signs of insufficient circulation was much higher in the etidocaine group, where rapid reductions in blood pressure frequently appeared after 5 to 10 min. The main difference as regards the analgesic potency between etidocaine adrenaline and the other anaesthetic agents used was a quicker onset and a greater degree of motor blockade. The early loss of muscular tone in combination with the sympathetic blockade may add to the peripheral pooling of blood in the extremities and explain the rapid fall in blood pressure. Due to this it was not regarded as safe to use etidocaine in higher concentrations without previous ephedrine premedication.

Blood pressure change in ephedrine-premedicated patients

Premedication with ephedrine seemed to stabilize the blood pressure and to reduce the number of patients with marked hypotension. Hence the need for further treatment was small and found mainly in the etidocaine groups. In spite of its subcutaneous administration immediately before anaesthesia, ephedrine seemed to elicit its pressor action soon after the epidural injection. This was specially noticeable with etidocaine, where ephedrine was able to prevent the rapid fall in blood pressure that often occurred without ephedrine premedication. The incidence of nausea was lower than without ephedrine premedication, probably due to the stable blood pressure, but may also be related to the central stimulating effects of ephedrine.

With ephedrine premedication the systolic blood pressure increased by 10 to 30 mmHg in some patients, usually during the early stage of analgesia. The marked increase in systolic blood pressure, from 155 to 220 mmHg, which occurred in one patient with etidocaine adrenaline was probably due to absorption of adrenaline, as the blood pressure increase was noted immediately after the epidural induction with a maximum after 5 min and was restored to a normal level in 15 min. The heart rate did not generally seem to be influenced by ephedrine, but the incidence of bradycardia requiring treatment with atropine was lower with ephedrine premedication. The increase in heart rate that occurred irrespective of ephedrine might be caused by the adrenaline in the local anaesthetic agent and/or may be secondary to the fall in blood pressure. Adrenaline added to the local anaesthetic agent has in epidural analgesia been reported to cause circulatory effects apart from those following the sympathetic blockade. Thus Bonica et al. (7, 8) have found in young volunteers that there was an increase in the circulatory variables such as cardiac output, stroke volume and heart rate and a greater decrease in the total peripheral vascular resistance if the local anaesthetic agent contained adrenaline than if it was used in plain solution. It has also been reported that the circulatory changes following epidural blockade with local anaesthetic agents in plain solution were similar to those following spinal analgesia, with less pronounced changes in central circulation (26). Ephedrine has been judged to be more adequate as a pressor agent during spinal analgesia than some other drugs, due to the combined positive ionotropic and vasoconstrictive effect (25, 27). It is not evident whether ephedrine has the same action during epidural analgesia with local anaesthetics containing adrenaline as interaction with adrenaline may occur. This will be elucidated further in a detailed study of the haemodynamic effect of ephedrine in connection with epidural blockade (16). In the present retrospective investigation all patients received epidural blockade with an anaesthetic solution containing adrenaline. In the patients not premedicated with ephedrine, there were in some cases circulatory failures that are likely to be caused not only by a fall in the peripheral resistance but also in stroke volume and cardiac output. In these cases the blood pressure was restored by ephedrine intravenously.

Conclusion

Ephedrine given subcutaneously prior to the epidural induction appears to be a suitable pressor agent to prevent hypotension in middle-aged and elderly patients during epidural blockade.

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