be made to ensure optimal intra-uterine and neonatal care because there may not be another successful pregnancy.

From a maternal point of view conservative management may be dangerous, as suggested by Sibai et al., but similar complications were not encountered in the present study. The explanation for this is unknown, but could be related to the intensive monitoring of the patients and prompt delivery when necessary. We conclude that conservative treatment of severe proteinuric hypertension at or after 24 weeks’ gestation is advantageous for the baby and carries little risk for the mother, provided that she can be intensively monitored in a special care unit.

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Plasma volume expansion in pregnancy hypertension

D. G. ALLEN, D. A. DAVEY, DENISE DACRE

Summary

Stabilised human serum 500 ml was infused intravenously over 90 minutes in 14 hypertensive women in late pregnancy, and the haemodynamic changes were investigated and compared with those in 7 similar women who were not treated. There was a significant mean increase of 1.85 l in plasma volume, a decrease in diastolic and systolic blood pressure, and an increase in central venous pressure (CVP), pulse pressure and pulse rate in the treated group at 2 hours but not in the control group. After 24 hours most of the observations were not significantly different from the pretreatment levels except the CVP and pulse rate measurements which were still significantly raised. The CVP measurements in the hypertensive women before treatment were relatively low compared with those reported in normal women in late pregnancy. It is suggested that there may be an under-filling of the circulation in pregnancy hypertension and that plasma volume expansion may have an important therapeutic effect by increasing cardiac output and renal and uterine blood flow.

Hypertension is a common complication of pregnancy and remains an important cause of perinatal morbidity and mortality. These patients appear to have relative hypovolaemia, generalised vasoconstriction, increased peripheral and systemic vascular resistance and a low cardiac output.

It has been suggested that at least in some cases these haemodynamic changes may be due to 'under-filling' of the circulation due to a low total circulating albumin with a low central venous pressure (CVP) and reduced venous return. It has also been suggested that this 'under-filling' of the circulation may be due to an increased capillary permeability to proteins resulting in leakage of albumin and fluid from the intravascular to the extravascular space. With the hypovolaemia and decreased cardiac output there may be a decrease in blood flow to both the kidneys and the uterus, which may have serious consequences.

The mean plasma volume of women with hypertension in pregnancy is approximately 15% (500-600 ml) less than that of normal pregnant women at comparable gestational age. In Europe it is generally believed that the hypovolaemia is secondary to vasoconstriction, whereas in some USA centres the reduction in blood volume is regarded as the primary change and vasoconstriction is considered to be secondary and patients may be treated with blood volume expansion. It is postulated that pre-eclampsia is primarily caused by failure of the blood volume to increase appropriately and that the relatively reduced blood volume results in a condition resembling 'chronic shock'. The 'chronic shock' results in poor organ and tissue perfusion, which may be exacerbated by the increased blood viscosity which occurs in pre-eclampsia.

Various workers have used plasma volume expanders in hypertensive patients and have claimed that renal and possible placental perfusion may be improved by such treatment. Some workers also believe that plasma volume expansion can reverse the disease process, at least temporarily, so that preg-
nancy may be continued long enough to allow fetal lung maturity to develop before delivery becomes imperative.

A study was undertaken to determine the effect of plasma volume expansion with 500 ml of stabilised human serum (SHS) infused over 90 minutes on the blood pressure, central venous pressure, plasma volume, capillary permeability and renal function in women with hypertension in pregnancy. It was also hoped to determine whether any of the adverse haemodynamic features of hypertensive pregnancy could be reversed by plasma volume expansion and whether there was a possible therapeutic role for this treatment.

Patients and methods

A prospective study was undertaken on 21 patients to determine the effect of plasma volume expansion on: (i) blood pressure; (ii) pulse rate; (iii) CVP; (iv) haematocrit; (v) plasma volume; (vi) capillary permeability; (vii) serum total protein and albumin; (viii) serum urea, urate and creatinine levels; (ix) 24-hour urine volume; and (x) creatinine clearance.

All patients selected for the study had: (i) a gestational age > 20 weeks; (ii) a diastolic blood pressure of > 90-119 mmHg; (iii) received no medication; (iv) no other obstetric complications or medical disorders; and (v) given free and informed consent.

Every third patient was treated as a control when the same observations were made under identical conditions but plasma volume expansion was not performed and the CVP was not measured. Patients were studied under standardised resting conditions over a 3-day period and the timetable of investigation is shown in Table I.

The plasma volumes were measured using an Evans blue dilution technique with the patients resting on their left side. Blood samples were collected at 0 (baseline), 10, 20, 30 and 60 minutes and the plasma volumes were calculated from the 10-minute sample. The remaining samples were taken to determine the disappearance rate of the Evans blue dye from the circulation as a measure of the capillary permeability to albumin. The Evans blue dye disappearance rate was calculated as the slope of regression line of the logarithm of the optical density of the Evans blue dye in each sample against time. The CVP was measured with a venous pressure manometer. The haematocrit in venous blood was measured in duplicate by Hawksley microcentrifuge. The serum creatinine and urine creatinine levels were determined by a standard auto-analyser technique (SMAC 12). Stabilised human serum (SHS) (Cape Western Province Blood Transfusion Service) 500 ml, containing total protein 50 ± 3 g/l and albumin 31 ± 2 g/l, was administered over 90 minutes to expand the plasma volume. The plasma volume measurements were taken immediately before infusion of SHS, 2 hours after the start of the infusion and again after 24 hours. The statistical differences of the observations before and after plasma volume expansion were analysed by paired t-tests. The differences between the plasma volume expansion group and the control groups were analysed by the unpaired t-test.

Results

The means of the initial blood pressure, pulse rate, CVP, plasma volume, Evans blue dye disappearance rate, plasma biochemistry and renal function measurements in the plasma volume expansion and control groups of patients were not significantly different. The changes in the mean values before and after infusion of SHS and in the control groups at 2, 4, 6, and 24 hours are shown in Tables II and III.

Blood pressure, pulse pressure and pulse rate

In the group given plasma volume expander there was a significant fall in diastolic blood pressure at 2 and 4 hours and in systolic blood pressure at 4 hours, and a rise in pulse pressure at 2 hours and in pulse rate at 2, 4 and 6 hours, but no significant changes were not in the control group. After 24 hours all the measurements had reverted to pretreatment levels with the exception of the pulse rate.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Group</th>
<th>Before</th>
<th>2 h</th>
<th>4 h</th>
<th>6 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>PVE</td>
<td>148 ± 16</td>
<td>142 ± 19</td>
<td>138 ± 22**</td>
<td>144 ± 20</td>
</tr>
<tr>
<td></td>
<td>CON</td>
<td>133 ± 20</td>
<td>131 ± 16</td>
<td>133 ± 24</td>
<td>129 ± 15</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>PVE</td>
<td>103 ± 9</td>
<td>89 ± 9**</td>
<td>92 ± 11**</td>
<td>100 ± 10</td>
</tr>
<tr>
<td></td>
<td>CON</td>
<td>100 ± 14</td>
<td>96 ± 14</td>
<td>98 ± 16</td>
<td>96 ± 14</td>
</tr>
<tr>
<td>PP (mmHg)</td>
<td>PVE</td>
<td>45 ± 17</td>
<td>53 ± 11*</td>
<td>46 ± 17</td>
<td>44 ± 16</td>
</tr>
<tr>
<td></td>
<td>CON</td>
<td>32 ± 10</td>
<td>34 ± 16</td>
<td>36 ± 9</td>
<td>32 ± 9</td>
</tr>
<tr>
<td>Pulse rate (/min)</td>
<td>PVE</td>
<td>73 ± 10</td>
<td>81 ± 10**</td>
<td>81 ± 10**</td>
<td>81 ± 9*</td>
</tr>
<tr>
<td></td>
<td>CON</td>
<td>78 ± 8</td>
<td>86 ± 8</td>
<td>80 ± 8</td>
<td>80 ± 10</td>
</tr>
</tbody>
</table>

Significance of difference from pre-treatment observations:
* P < 0.05; ** P < 0.01
** P < 0.001
*** P < 0.0001

PVE = plasma volume expanded; CON = control; SBP = systolic blood pressure; DBP = diastolic blood pressure; PP = pulse pressure.
Central venous pressure

The means and ranges of CVP measurements before and 2, 4, 6 and 24 hours after plasma volume expansion were respectively 2.3 (1.0-4.5), 5.2 (2.0-11.0), 5.8 (2.0-14.0), 6.7 (2.0-15.0), and 6.3 (1.5-14.0) cm water. The means of the post-treatment measurement, including the 24-hour observation, were all significantly raised above the mean pretreatment measurement ($P < 0.001$).

Plasma volume and haematocrit

The increase of 1.85 l in plasma volume at 2 hours after infusion of SHS 500 ml was highly significant but both the plasma volume and haematocrit measurements had reverted to pretreatment levels after 24 hours.

Serum total protein level, albumin and protein capillary permeability

There were no significant changes in capillary permeability to protein as measured by the Evans blue dye disappearance rate after 2 and 24 hours and no differences in serum total protein level and albumin after 24 hours in the plasma-expanded and control groups.

Renal function

The serum urine, urate and creatinine levels and creatinine clearance were not significantly different after 24 hours in both the volume-expanded and control groups.

Discussion

Pregnant women with chronic or gestational hypertension have contracted plasma volumes. A low plasma volume is related to low birth weight and a poor outcome of pregnancy. The relationship of blood volume, total vascular capacity and CVP has been inadequately studied in both normotensive and hypertensive pregnant women. Colditz and Josey reported that the mean CVP in non-pregnant patients was 9 cm water and that it fell progressively during pregnancy to 3.8 cm water in the third trimester. Cloeren et al. found a mean CVP of -4.2 cm water in 15 hypertensive patients which was increased to a mean of -2.4 cm water after plasma volume expansion. In this study the mean value of CVP before expansion was -2.3 cm water, which increased after volume expansion to approximately +6.8 cm water and was maintained for at least 24 hours. These findings suggest that hypertensive patients may have a reduced CVP and that there may be 'under-filling' of the circulation which can be reversed by plasma volume expansion with SHS 500 ml.

The fall in diastolic blood pressure in response to plasma volume expansion is surprising and suggests that not only is there a passive increase in the vascular capacity but also an active arterial or arteriolar vasodilatation. Botha et al. and Pace-Asciak et al. have shown that distention and stretch cause a release of prostacycline from the rat's aorta and that this effect is increased in hypertensive rats. The fall in blood pressure during plasma volume expansion may thus be caused by the local release of prostacycline as a direct result of distension of the arteries and arterioles. The fall in blood pressure could also be caused by a vasodilating agent in SHS. In plasma protein extracts a vasodilating agent has been identified corresponding to a protein of molecular weight of approximately 100 000.$^{21}$ The effect of this agent, however, is short-lived and disappears 2-3 minutes after stopping the infusion.

The increase in pulse pressure together with an increased pulse rate immediately after the infusion of SHS suggests an increased cardiac output which may have an important beneficial effect by increasing renal and uterine blood flow. The creatinine clearance rate and serum creatinine and urea levels, however, were unchanged 24 hours after plasma volume expansion and it is possible that the beneficial changes are relatively short-lived and are lost by 24 hours after a 90-minute plasma volume expansion.

The mean increase in plasma volume of 1.85 l 2 hours after infusion of SHS 500 ml suggests that although SHS is reputedly iso-osmotic it does increase the plasma oncotic pressure and causes the transfer of additional fluid from the extravascular to the intravascular space. The lack of change in Evans blue dye disappearance rate after infusion in the plasma-expanded and control groups, however, is not surprising. The reduction in plasma volume may nevertheless be due to an increased capillary permeability to albumin in women with hypertension in pregnancy. It is possible that this increase may be restricted to hypertensive women with proteinuria and it may be important in future investigations to differentiate between non-proteinuric and proteinuric forms of pregnancy hypertension.

The effect of plasma volume expansion in pregnancy hypertension may be important therapeutically by lowering of blood pressure but more particularly by increasing cardiac output and increasing renal and uterine blood flow. Expansion or restoration of blood volume may also be essential in the management of severe hypertension in pregnancy where the use of antihypertensive agents to produce vasodilatation may

<table>
<thead>
<tr>
<th>TABLE III. PLASMA VOLUME, HAEMATOCRIT AND SERUM TOTAL PROTEIN AND ALBUMIN LEVELS IN THE TWO GROUPS (MEAN ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurement</td>
</tr>
<tr>
<td>Plasma volume (l)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Haematocrit (%)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Serum protein (g/l)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Serum albumin (g/l)</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

*** $P < 0.001$

PVE = plasma volume expanded; CON = control.
cause a fall in venous return and hence in cardiac output unless the CVP and blood volume are restored by intravenous fluid infusion. This study suggests that this potential beneficial effect is relatively short-lived, and that it may be necessary to give some form of continuous infusion. SHS may also not be the optimal solution for plasma volume expansion, and a better preparation may be a hyperosmotic solution such as 20% albumin solution which may produce a greater increase in plasma oncotic pressure and a larger and more sustained increase in plasma volume.

We wish to acknowledge the expert laboratory assistance of Miss Dot Steyn and Miss Barbara Werb. This study was supported by the South African Medical Research Council.

REFERENCES