ATTENUATION OF THE PRESSOR RESPONSE TO TRACHEAL INTUBATION BY MAGNESIUM SULPHATE WITH AND WITHOUT ALFENTANIL IN HYPERTENSIVE PROTEINURIC PATIENTS UNDERGOING CAESAREAN SECTION

W. B. ASHTON, M. F. M. JAMES, P. JANICKI AND P. C. UYS

SUMMARY

The pressor response to tracheal intubation is known to be exaggerated in patients with gestational proteinuric hypertension (GPH). We have studied the effect of pretreatment with magnesium sulphate 40 mg kg\(^{-1}\) or 30 mg kg\(^{-1}\) with alfentanil 7.5 \(\mu\)g kg\(^{-1}\) on this pressor response in 38 patients with moderate to severe GPH. The magnesium–alfentanil combination produced better control of arterial pressure and heart rate than magnesium alone, although both techniques provided good cardiovascular control. There was no significant difference in fetal outcome between groups. Both pretreatment methods produced satisfactory control of catecholamine release.

KEY WORDS


There is a marked pressor response to tracheal intubation in the hypertensive pregnant patient, with increases in systemic and pulmonary arterial pressures and pulmonary capillary wedge pressure [1, 2]. There is also an associated increase in intracranial pressure and in the risks of cerebral haemorrhage and cardiac failure with pulmonary oedema; as a result, morbidity and mortality in both mother and child are increased [3]. There have been several attempts to attenuate these haemodynamic responses using high- and low-dose opioids, adrenoceptor blockers, vasodilators, and topical and i.v. anaesthetics. None of these techniques appears to be entirely satisfactory for patients with gestational proteinuric hypertension (GPH) [4]. Alfentanil appears to be the most promising of the opioids, with its rapid onset and short duration of action [5], and has been shown, at a dose of 10 \(\mu\)g kg\(^{-1}\), to obtund the pressor response whilst producing minimal fetal depression in normal pregnancies [6]. Caution is advocated regarding possible detrimental effects on the fetus [7] and the mother [8].

Magnesium sulphate (MgSO\(_4\)) has been shown not only to inhibit catecholamine release [9] but also to control the pressor response to tracheal intubation [10]. Its role in the management of GPH has been established for some time [11], and it has been shown to antagonize the action of several vasoconstrictor substances in pregnant ewes [12]. We have shown previously [13] that both alfentanil 10 \(\mu\)g kg\(^{-1}\) and MgSO\(_4\) 40 mg kg\(^{-1}\) produced adequate control of arterial pressure at tracheal intubation in GPH, but there were disadvantages with both agents. In the alfentanil-treated group, marked neonatal depression occurred and 25% of patients had failure of adequate control of arterial pressure (defined as a systolic arterial pressure > 180 mm Hg sustained for 2 min or more after intubation). Good control of arterial pressure was achieved in all but two patients in the MgSO\(_4\) group, but with significant tachycardia. As the two drugs act via different
mechanisms, it is possible that a combination of both drugs in reduced doses may produce the benefits of both, with fewer side effects. As MgSO₄ had proved the best of the agents tested previously, we have compared the effects of MgSO₄ with a combination of MgSO₄ and alfentanil on the cardiovascular responses to tracheal intubation in patients with severe GPH requiring Caesarean section under general anaesthesia. As both magnesium [10] and alfentanil [14] have been shown independently to inhibit the release of catecholamines at the time of tracheal intubation, it was considered that the combination could prove effective, not only in reducing the hypertensive response to intubation, but also in inhibiting release of catecholamines. The dose of the two agents was chosen after a preliminary investigation in non-pregnant subjects showed that magnesium 30 mg kg⁻¹ with alfentanil 5 μg kg⁻¹ was not significantly better than alfentanil alone.

**PATIENTS AND METHODS**

The study was approved by the Human Ethics Committee of the University of Cape Town, and written informed consent was obtained from all participants. Entry and exclusion criteria for the study were identical to those used for our previous investigation, as were pre-anaesthetic management regimens [13]. Patients were allocated randomly to one of two groups: group 1 received MgSO₄ 40 mg kg⁻¹ and group 2 received MgSO₄ 30 mg kg⁻¹ + alfentanil 7.5 μg kg⁻¹.

On arrival of the patient in the operating theatre suite, an indwelling cannula was inserted under local anaesthetic into a vein in the antecubital fossa for blood sampling, on the arm opposite to that in which the i.v. drip was sited. At this stage, blood was taken for baseline estimations. This sample was analysed for serum urea and electrolytes, calcium, magnesium and catecholamine concentrations. All subsequent maternal samples were analysed for magnesium, alfentanil and catecholamine concentrations. Catecholamine concentrations were measured by electrochemical detection after separation with reverse phase HPLC using dihydrobenzylamine as internal standard [15]. The coefficient of variation was 7.9% for noradrenaline and 8.7% for adrenaline, and the limit of sensitivity was 10 pg ml⁻¹. Alfentanil concentrations were measured by gas chromatography. Continuous, non-invasive arterial pressure monitoring and anaesthetic techniques were similar to those described previously [13].

A second blood sample was obtained 1 min after completion of laryngoscopy and intubation, taken as the time when the cuff of the tracheal tube was inflated. Anaesthesia was maintained for 5 min before the start of surgery with 50% nitrous oxide and 0.5% halothane in oxygen with ventilation adjusted to ensure normocapnia, during which time arterial pressure was measured continuously. Neuromuscular block was maintained with an infusion of suxamethonium 4–8 mg min⁻¹ and neuromuscular function monitored using a nerve stimulator.

At the end of the 5 min monitoring period, during which time the patient had been cleaned and draped, another venous blood sample was obtained. Surgery then commenced and the times from skin incision to delivery, and uterine incision to delivery were noted. After delivery of the infant, when the rectus muscle was being sutured, the suxamethonium infusion was discontinued and at the onset of spontaneous breathing, another sample of maternal blood was obtained.

Cardiovascular responses to surgery were noted. At delivery of the infant, cord blood was sampled for serum concentrations of magnesium and alfentanil where appropriate, and for fetal acid–base status. After delivery, neonates were scored on the Apgar system at 1 and 5 min, by a paediatrician who was blinded to the study drug given. The paediatrician also recorded what resuscitative measures had been necessary, including the use of naloxone and the response to this drug.

Statistical analysis was performed using Statgraphics (Version 4.0) statistical package running under MS-DOS (version 3.3) on an IBM-compatible AT personal computer. Between-group comparisons were performed using Student's t test, Wilcoxon rank sum and Fisher's Exact tests where appropriate. The sample size was determined as the smallest necessary to detect a 15-mm Hg between-group difference within the anticipated systolic arterial pressure range with an estimated SD of 20 mm Hg for each group (α = 0.05; β = 0.1). Within-group comparisons were performed using analysis of variance for repeated measures with the use of 95% confidence intervals to identify significantly different samples. All maternal data were grouped and analysed by regression analysis for association between the
Table I. Maternal characteristics and arterial pressure on admission (mean (sd)). Emerg. = Emergency procedure; Elect. = elective procedure. No significant differences between groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Gestational age (weeks)</th>
<th>Emerg. (No.)</th>
<th>Elect. (No.)</th>
<th>Arterial pressure (mm Hg)</th>
<th>Systolic</th>
<th>Diastolic</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (n = 19)</td>
<td>25.6 (6.7)</td>
<td>72.9 (15.3)</td>
<td>32.5 (4.1)</td>
<td>19</td>
<td>0</td>
<td>158.9 (21.1)</td>
<td>108.4 (14.8)</td>
<td>123.7 (17.6)</td>
<td></td>
</tr>
<tr>
<td>2 (n = 19)</td>
<td>26.3 (4.9)</td>
<td>77.6 (13.9)</td>
<td>32.1 (3.9)</td>
<td>18</td>
<td>1</td>
<td>167.9 (22.7)</td>
<td>108.9 (13.6)</td>
<td>132.9 (21.7)</td>
<td></td>
</tr>
</tbody>
</table>

Table II. Preoperative medication used in the 12 h before surgery to control the symptomatology of GPH in the two groups, and steady state arterial pressures in the operating room (mean (sd)). No significant between-group differences

<table>
<thead>
<tr>
<th>Group</th>
<th>Nil (No.)</th>
<th>MgSO₄ (No.)</th>
<th>Aldomet (No.)</th>
<th>Nifedipine (No.)</th>
<th>β-Blocker (No.)</th>
<th>Hydralazine (No.)</th>
<th>AP (mg Hg)</th>
<th>Systolic</th>
<th>Diastolic</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (n = 19)</td>
<td>3</td>
<td>11</td>
<td>3</td>
<td>6</td>
<td>0</td>
<td>5</td>
<td>181.6 (19.8)</td>
<td>110.5 (12.5)</td>
<td>142.2 (18.0)</td>
<td></td>
</tr>
<tr>
<td>2 (n = 19)</td>
<td>4</td>
<td>9</td>
<td>6</td>
<td>5</td>
<td>2</td>
<td>4</td>
<td>174.1 (24.9)</td>
<td>105.2 (9.9)</td>
<td>133.0 (17.5)</td>
<td></td>
</tr>
</tbody>
</table>

Table III. Magnesium and catecholamine concentrations at various times (mean (sd)). No significant differences between groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>After intubation</th>
<th>Before incision</th>
<th>After delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnesium (mmol litre⁻¹)</td>
<td>1.39 (0.43)</td>
<td>2.41 (0.80)</td>
<td>1.92 (0.56)</td>
<td>1.31 (0.36)</td>
</tr>
<tr>
<td>Noradrenaline (pg ml⁻¹)</td>
<td>802 (646)</td>
<td>636 (434)</td>
<td>570 (473)</td>
<td>715 (495)</td>
</tr>
<tr>
<td>Adrenaline (pg ml⁻¹)</td>
<td>263 (243)</td>
<td>261 (291)</td>
<td>187 (278)</td>
<td>423 (385)</td>
</tr>
</tbody>
</table>

Severity of cardiovascular responses and maternal age, parity and initial diastolic pressure. The null hypothesis was rejected at $P < 0.05$.

RESULTS

Subjects in both groups were well matched in respect of age, weight, gestational age and cardiovascular variables (table I) and there were no significant differences in routine biochemical variables between the groups.

After arterial pressure had been stabilized in the operating theatre, the cardiovascular data of the two groups were not significantly different (table II) and the use of antihypertensive medications within 12 h of surgery was basically similar in both groups.

Only one patient suffered a convulsion before admission to the study and she was allocated to group 2. Of the 20 patients who had received MgSO₄ before entry to the study, one patient had a serum concentration of magnesium within the normal range (0.75–1.0 mmol litre⁻¹), and only one had a value generally regarded as therapeutic (> 2 mmol litre⁻¹). In the remainder, the serum concentrations of magnesium varied between 1 and 2 mmol litre⁻¹ (table III). There was no statistically or clinically significant difference between the values in the two groups, despite the different bolus doses of MgSO₄. The greatest serum concentration of magnesium recorded after administration of MgSO₄ was 3.65 mmol litre⁻¹ and after delivery the greatest value recorded was 2.35 mmol litre⁻¹. The mean serum concentration
of magnesium at the end of the procedure was less than that associated with neuromuscular impairment (table III), and no difficulties were experienced in re-establishing neuromuscular function at the end of the procedure.

Systolic, diastolic and mean arterial pressures decreased significantly after induction in both groups, and there was no significant difference in the magnitude of the change in the two groups. There was no statistically significant mean increase in arterial pressure at tracheal intubation, but there was significantly better control of systolic arterial pressure (SAP) in group 2 mothers at laryngoscopy and at 3 and 4 min afterwards (fig. 1). Systolic arterial pressure remained less than baseline from induction until the onset of surgery in both groups. Similar trends occurred in mean and diastolic arterial pressures, with significant between-group differences at the same times as for systolic pressure changes. There were no serious hypotensive episodes; the least mean arterial pressure was 70 mm Hg, in a group 2 subject at 2 min after intubation. Arterial pressure control was also analysed using our previous criteria [13] for inadequate control, defined as an increase in systolic arterial pressure to > 180 mm Hg for 2 min or more. Satisfactory arterial pressure control was achieved in both groups, with only one mother in group 2 compared with three in group 1 showing inadequate control (ns between groups). Only one patient (in group 1) showed an increase in systolic pressure to a value greater than her initial pressure before induction. There was no correlation between the severity of the hypertensive response to tracheal intubation and patient age, parity or initial diastolic arterial pressure.

Heart rates increased significantly after induction in both groups, but absolute values and the magnitude of the increase with induction were significantly less in group 2 (fig. 2). Heart rate remained greater than before induction until 4 min after tracheal intubation in group 1, but in group 2 heart rate was significantly different from baseline only immediately after intubation. Heart rate did not increase further in either group during or after laryngoscopy, but heart rate was significantly less in group 2 than in group 1 immediately after laryngoscopy had been completed. Consequently, the rate–pressure products were significantly smaller in group 2 during this period. There were no arrhythmias in either group. Three difficult intubations were encountered, with laryngoscopy to intubation times of 25 s or greater. These were all in group 2 and not associated with remarkable changes in arterial pressure.

The mean baseline serum concentrations of catecholamines were increased in both groups (table III), although there was considerable

![Figure 1](image.png)

**Fig. 1.** Mean (±SD) systolic arterial pressures (SAP) in the magnesium (■) and magnesium plus alfentanil (●) groups. Times refer to time from induction and administration of the study drug. OR = Stable value with the patient settled in theatre; BL = value before laryngoscopy, after induction and administration of study drug; PL = peak values during or after laryngoscopy and intubation.

*Statistically significant differences between groups (P < 0.05). Systolic pressure was significantly different from baseline in both groups at all shown times after induction.
variability in the data. Thirteen patients in group 1 and 15 in group 2 had serum concentrations of catecholamines greater than the normal range for our laboratory (adrenaline 10–80 pg ml⁻¹, noradrenaline 200–400 pg ml⁻¹) before induction of anaesthesia. However, there were no significant differences in absolute values, or in the changes in adrenaline or noradrenaline concentrations between groups 1 and 2 at any time. It is of particular interest that there was no overall increase in the concentration of each catecholamine at tracheal intubation. There was also no correlation between arterial pressure changes and changes in serum concentrations of catecholamines. However, four patients in each group showed increases in their serum concentrations of noradrenaline after tracheal intubation, and these included the worst controlled patients in each group. Both groups showed similar increases in serum concentrations of catecholamines towards the end of the procedure when the plasma concentrations of both magnesium and alfentanil were declining, and tracheal extubation was associated with significant increases in arterial pressure and heart rate.

Maternal mean serum concentrations of alfentanil in group 2 mothers 1 min after tracheal intubation and after delivery were 62.8 (SD 20.6) ng ml⁻¹ and 14.6 (5.4) ng ml⁻¹, respectively, and the concentration in the mixed cord blood of their infants was 8.3 (4.9) ng ml⁻¹. There was no correlation between initial maternal alfentanil concentrations and umbilical concentrations, although there was a weak correlation (r = 0.41) between post-delivery maternal concentrations and those in the umbilical artery. There was no significant difference between groups in the use of, or response to, naloxone in the neonates.

The values of the various neonatal variables recorded are shown in table IV. There was no statistically significant difference between the groups in any of the variables. There was no
correlation between any of the alfentanil or magnesium measurements and any measurement of neonatal well-being.

**DISCUSSION**

In our previous study [13], we concluded that MgSO₄ was superior to either lignocaine or alfentanil for attenuation of the pressor response to tracheal intubation. In this study, we have confirmed that MgSO₄ was highly satisfactory for this purpose, but it appeared that the combination of MgSO₄ and alfentanil, both in reduced doses, was superior to the use of each agent alone, in terms of both maternal arterial pressure control and changes in heart rate. This combination did not appear to have any significant disadvantage for these compromised fetuses. There was no evidence that the reduction in arterial pressure compromised the fetus, and it has been shown that magnesium-induced hypotension does not reduce uterine blood flow [16].

These results show better cardiovascular control than those reported by Rout and Rocke [17] using either fentanyl or alfentanil in combination with droperidol and lignocaine. They found significant increases in both systolic and diastolic pressures and heart rate after tracheal intubation. However, they chose a more severely ill group of patients in that all their subjects were older than 25 yr, and all had diastolic arterial pressures > 110 mm Hg whereas, in our study, 13 of the patients were younger than 25 yr and nine had diastolic pressures between 90 and 110 mm Hg. We were unable to find any evidence that patient age, resting diastolic arterial pressure or parity had any influence on the severity of the response, in contradistinction to other reports [2, 3, 17].

Dann, Hutchinson and Cartwright [7] reported the absence of neonatal effects of maternally administered alfentanil, and hypothesized that the effect of alfentanil on the neonate would be minimal because of its short half-life. This study has confirmed that, in the hypertensive, proteinuric, pregnant patient, rapid elimination of alfentanil occurred, and that very low fetal concentrations of alfentanil may be anticipated. We did not measure free alfentanil concentrations, but it seems likely that these premature neonates had less plasma protein binding of alfentanil than normal neonates, who also have a smaller percentage of alfentanil binding than adults [8]. For any given concentration of alfentanil, a greater effect may therefore be anticipated in the premature neonate. Redfern and colleagues [8] reported severe depression in a neonate with a total plasma concentration of alfentanil 22.4 ng ml⁻¹ which was considerably greater than the concentrations observed in our neonates. The smaller concentrations measured in the neonates in our study presumably account for the apparent lack of alfentanil-induced depression. However, the margin of safety appears to be rather small, and this may explain the significant depression which we observed in our previous study with only a slightly greater dose of alfentanil (10 μg kg⁻¹) [13].

It is interesting that there were no inter-group differences in catecholamine concentrations. There was no mean increase in catecholamine concentrations in either group, which contrasts with reports of 21% [18] and 28% [19] increases in noradrenaline in normal patients and a 33% increase in GPH patients [19]. The lesser arterial pressures and heart rates in group 2 were clearly not attributable to differences in release of catecholamines. This is not entirely surprising, as the concentrations of circulating noradrenaline required to exert measurable haemodynamic effects are in the range 1500–2000 pg ml⁻¹ [20], values which were observed in only one patient in this study. Presumably, therefore, the small increases in arterial pressure occurring after intubation in both groups were the result of sympathetic nerve stimulation. Mean plasma concentrations of adrenaline were unchanged in both groups after tracheal intubation, and the lower heart rate seen in group 2 was presumably caused by the direct effect of alfentanil on heart rate.

**ACKNOWLEDGEMENT**

This study was supported by a research grant from the South African Medical Research Council.

**REFERENCES**


