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Intravenous and intramuscular magnesium sulphate regimens in severe pre-eclampsia

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Patients with severe pre-eclampsia were randomised to receive magnesium sulphate according to an intramuscular (IM) (*N* = 9) or an intravenous (IV) (*N* = 8) regimen. The IM regimen consisted of a loading dose of 14 g (4 g IV and 10 g IM) followed by 5 g 4-hourly. Patients given the IV regimen received a 6 g IV loading dose followed by a maintenance infusion of 2 g/h. Clinical outcome, laboratory parameters and serum magnesium levels were recorded for both groups.

There were no significant differences between groups with regard to clinical outcome of either mother or child. Similar average serum magnesium concentrations were produced by the regimens the only significant difference was that fluctuations in magnesium levels were greater with the IM than the IV regimen. None of the patients had seizures despite levels mostly below 2 mmol/l.

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Magnesium sulphate ($MgSO_4$) is the anticonvulsant most widely used in the USA and South Africa for the management of severe pre-eclampsia. It is given parenterally, usually according to one of two popular regimens: the intramuscular (IM) regimen introduced by Pritchard[1] and a continuous intravenous (IV) infusion described by Zuspan.[2] Sibai *et al.*[3] have reported that lower serum magnesium values are achieved with Zuspan's regimen (maintenance dose 1g/h) than with Pritchard's regimen. Given that Sibai *et al.*[4] had previously found that 8 of 9 convulsing patients had low levels of serum magnesium after receiving Zuspan's regimen, they concluded that an IV maintenance dose of 1 g/h was insufficient to prevent the occurrence of seizures in some pre-eclamptic patients. They thus recommend an IV maintenance dose of 2 g/h.[3]

The purpose of this prospective study was to compare the clinical outcome as well as the magnesium levels obtained in the treatment of severe pre-eclampsia with the IM regimen of Pritchard and an IV regimen with maintenance doses of 2 g/h.

Subjects and methods

Seventeen women with severe pre-eclampsia and imminent eclampsia were studied at King Edward VIII (KEH) Hospital in Durban. This hospital is a tertiary referral centre for the coastal region of Natal and serves an indigent population from poor socio-economic conditions. Delivery of 14 000 high-risk patients is conducted each year and 18% of all obstetric admissions have some degree of hypertension.

Patients eligible for the trial had proteinuria of at least 1+ assessed by a semiquantitative 'dipstick' method (Ames) and diastolic blood pressures of 110 mmHg or more which did not settle during a 4-hour observation period. Patients with hypertension and proteinuria who had additional symptoms or signs such as persistent headache, visual disturbances, epigastric pain, increased patellar reflexes and clonus, were considered to have impending eclampsia — 2 of the 8 women in the IV group and 4 of the 9 women in the IM group.

After Ethics Committee approval was received, patients were randomly allocated to receive either IM or IV $MgSO_4$. Those receiving the IM regimen (*N* = 9) were given 4 g $MgSO_4$ in 200 ml normal saline as an infusion over 15 minutes and simultaneously given 5 g $MgSO_4$ IM in each buttock. Thereafter, every 4 hours an additional 5 g $MgSO_4$ were given in alternate buttocks.

Eight patients received continuous IV $MgSO_4$. A loading dose of 6 g in 200 ml normal saline was infused over 15 minutes, followed immediately by a maintenance dose of 2 g/dl/h given via a controlled infusion pump.

In all patients the patellar reflexes and respiratory rate were noted every 4 hours. When either was suppressed, or when the urine output was less than 30 ml/h over the preceding 4 hours, $MgSO_4$ was discontinued. $MgSO_4$ was discontinued after 24 hours of therapy, providing delivery had occurred.

Obstetric management continued according to a standard protocol previously described.[5] If the diastolic blood pressure reached 115 mmHg, then 6,25 mg dihydralazine in 10 ml normal saline was infused over a period of at least 5

minutes. High blood pressure was only lowered after the correction of hypovolaemia with Ringer's lactate solution. Hypovolaemia was assessed by central venous pressure (CVP) which was measured by inserting a central line through a large vein in the antecubital fossa. The position of the tip of the CVP catheter was checked by radiological examination of the chest.

Various maternal investigations were carried out, including measurement of haematocrit, platelet count, serum creatinine (on entry), serum albumin and calcium levels and 24-hour urinary protein. Maternal convulsions, if they occurred, were noted. Details of delivery, gestational age and fetal weight, and Apgar scores were also recorded.

Serum magnesium levels were measured at baseline and repeated every 30 minutes for the first 3 hours after the loading dose. They were subsequently measured at 5, 7, 9, 11, 15 and 19 hours. Blood was taken through the CVP line with allowance made for the dead space. Samples were centrifuged at once and serum was analysed the following day by the routine hospital laboratory, using a dye-binding procedure with Calmagite (Beckman Sychron CX5).

Serum magnesium levels versus time were plotted for all patients and the following values were recorded for each: $c_{max\,1}$ — the first peak level recorded; $t_{max\,1}$ — the time of this peak; $c_{max\,2}$ — the highest overall peak in the first 12 hours (in some cases equal to $c_{max\,1}$); $t_{max\,2}$ — the time of this peak (in some cases equal to $t_{max\,1}$); c_{min} — the lowest level recorded in the first 12 hours; t_{min} — the time of this trough; and $\Delta c_p = c_{max\,2} - c_{min}$ — the maximum fluctuation in serum levels during the first 12 hours.

All these values were compared between patients from the IM and IV groups in an attempt to quantitate whether or not any differences resulted from the two regimens.

Differences between the IM and IV groups were assessed by means of the unpaired Student's *t*-test. A *P*-value of 0,05 or less was considered to represent a statistically significant difference between groups.

Changes in both serum albumin and serum calcium levels from 0 - 11 hours and 0 - 19 hours within both the IM and IV groups were assessed by the paired Student's *t*-test. The Bonferroni adjustment was applied and a *P*-value of 0,025 or less was considered significant.

Results

Demographic details, blood pressure values and results of investigations for the mothers, as well as the fetal weights, gestational ages and Apgar scores of the babies, are presented in Table I. The only statistically significant differences between the IM and the IV groups were in the baseline serum albumin levels ($P = 0,034$) and the serum calcium levels at 19 hours ($P = 0,032$). The serum creatinine values in both groups were similar, except for 1 patient in the IV group with a value of 229 µmol/l. Dosing of this patient was stopped after 3 hours. Serum albumin levels fell significantly between 0 and 11 hours in both the IM ($P = 0,004$) and IV groups ($P = 0,0024$) as well as between 0 and 19 hours ($P = 0,008$ IM, $P = 0,0075$ IV). There was also a significant fall in serum calcium levels between 0 and 11 hours ($P = 0,004$ IM; $P = 0,0021$ IV) and between 0 and 19 hours ($P = 0,0004$ IM; $P = 0,0025$ IV).

Table I. Maternal and neonatal data (means ± SD)

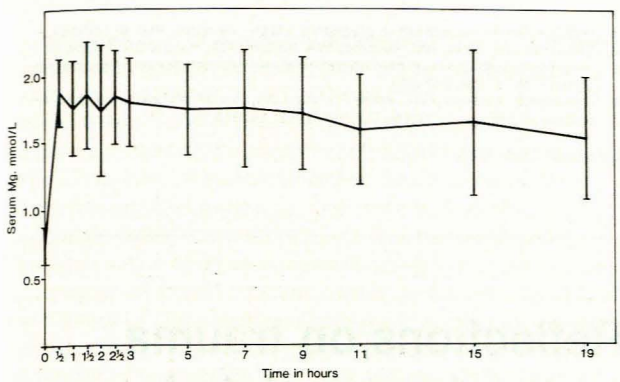
Group	IM $MgSO_4$ ($N = 9$)	IV $MgSO_4$ ($N = 8$)
Patient details		
Age (yrs)	21,4 ± 4,5	23,6 ± 6,8
Weight (kg)	73,8 ± 10,1	73,5 ± 4,8
Systolic BP (mmHg)	169,0 ± 13,6	163,0 ± 13,9
Diastolic BP (mmHg)	114,0 ± 7,3	113,0 ± 4,6
Serum creatinine (µmol/l)	59,3 ± 10,7	87,4 ± 60,3
24-h urinary protein (g/l)	1,1 ± 1,1 ($N = 8$)	1,0 ± 0,9 ($N = 7$)
Haematocrit (%)	29,2 ± 3,3	31,2 ± 3,6
Platelet count (x 10^9/l)	259,0 ± 72,1	207,0 ± 64,8
Delivery time relative to start of $MgSO_4$ (h)	5,8 ± 4,2	5,3 ± 3,1
Serum albumin (g/l)		
0 h	26,3 ± 3,0	22,0 ± 4,0
11 h	20,0 ± 3,0 ($N = 8$)	18,0 ± 3,0 ($N = 6$)
19 h	20,0 ± 4,0 ($N = 7$)	16,0 ± 3,0 ($N = 5$)
Serum calcium (mmol/l)		
0 h	2,01 ± 0,10	1,96 ± 0,10
11 h	1,58 ± 0,20 ($N = 8$)	1,51 ± 0,20 ($N = 6$)
19 h	1,66 ± 0,15 ($N = 7$)	1,44 ± 0,15 ($N = 5$)
Details of baby		
Weight (kg)	2,6 ± 0,9	2,4 ± 0,8
Gestational age (wks)	35,9 ± 3,5	34,6 ± 3,2
Apgar score		
1 min	6,0 ± 3,0	6,0 ± 3,0
5 min	8,0 ± 3,0	8,0 ± 4,0

Various other details for the two groups can be seen in Table II. None of the patients had seizures. Only 1 patient (in the IV group) had clinical signs of magnesium toxicity (oliguria and decreased patella reflexes) which necessitated the cessation of $MgSO_4$ therapy after 7 hours. The serum magnesium level in this patient at 7 hours was 1,97 mmol/l (baseline serum magnesium level 0,76 mmol/l). In another patient (mentioned above) $MgSO_4$ was stopped because of renal failure. There were no differences between groups with regard to mode of delivery or fetal outcome. Seven out of 8 women in the IV group, as opposed to 2 out of 9 in the IM group, had antenatal medication. However, in the absence of pre-pregnancy or post-delivery blood pressure measurements, it was assumed that all patients had proteinuric pregnancy-induced hypertension or essential hypertension with superimposed pre-eclampsia. Figs 1 and 2 show that similar average serum magnesium concentrations were produced by the two regimens.

Table II. Further details of patients in the IM and IV groups

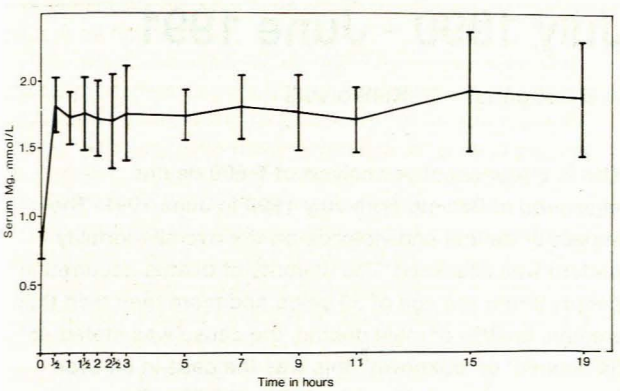
	IM $MgSO_4$ ($N = 9$)	IV $MgSO_4$ ($N = 8$)
Maternal convulsions	0	0
Clinical signs of magnesium toxicity	0	1
Normal vaginal delivery	5	4
Assisted vaginal delivery	1	0
Caesarean section	3	4
Live births	9*	7
Fresh stillbirths	1	1
Antenatal medication†	2	7
Intrapartum medication‡	6	5

* One patient had twins.
† This consisted of methyldopa and dihydralazine, except in the case of 1 patient in the IV group who also received dexamethasone and phenobarbitone.
‡ Dihydralazine.



Number of sample points between 0 and 19 hours: 9, 9, 9, 7, 9, 8, 9, 8, 8, 7, 8, 5 and 4.

Fig. 1. Mean ± SD serum magnesium levels for patients on the IM regimen.



Number of sample points between 0 and 19 hours: 8, 8, 8, 8, 8, 8, 8, 7, 7, 7,5, 3 and 4.

Fig. 2. Mean ± SD serum magnesium levels for patients on the IV regimen.

The doses of $MgSO_4$, the mean values of the maximum and minimum serum concentrations and the maximal fluctuations in serum concentrations are presented in Table III.

Table III. Magnesium doses and maximum and minimum serum levels in patients receiving the IM and IV regimens

	IM $MgSO_4$	IV $MgSO_4$
Magnesium doses		
Loading dose (g)	14	6
Maintenance dose	5 g/4 h	2 g/h
Total dose up to 12 hours (g)	24	30
Serum magnesium levels and times (means ± SD)		
Baseline level (mmol/l)	0,74 ± 0,14	0,80 ± 0,12
$c_{max\,1}$ (mmol/l)	2,07 ± 0,25	1,96 ± 0,27
$t_{max\,1}$ (h)	1,52 ± 1,12	0,94 ± 0,90
c_{min} (mmol/l)	1,47 ± 0,36	1,57 ± 0,19
t_{min} (h)	5,89 ± 3,90	3,40 ± 2,54
*Δ c_p (mmol/l)	0,67 ± 0,27	0,37 ± 0,18

*P = 0,026.
$c_{max\,1}$ — the first maximum level recorded, $t_{max\,1}$ — the time of the first maximum level, c_{min} — the lowest level recorded in the first 12 hours, t_{min} — the time of this trough, Δ c_p — the highest peak in the 1st 12 hours minus the lowest trough, i.e. the maximal fluctuation in levels in the 1st 12 hours.

There were no statistically significant differences between the maximum and minimum serum concentrations produced by the two regimens or the times at which these values were reached. However comparison of values of ΔC_p (the highest peak minus the trough) revealed that fluctuations in serum magnesium levels were significantly greater with the IM than with the IV regimen (P = 0,026).

Discussion

This study, which set out to compare the IM $MgSO_4$ regimen of Pritchard[1] with an IV regimen[3] using a maintainance dose of 2 g/h in patients with severe pre-eclampsia, revealed very little difference between the groups. The clinical outcome of the patients and their babies was similar and none of the patients had convulsions.

The fact that serum calcium levels fell significantly during magnesium treatment was consistent with the findings of the other workers who have shown a similar reciprocal relationship between the ions.[3] In the present study, however, serum calcium levels were significantly lower in the IV group after 19 hours than in the IM group.

The average maintenance serum magnesium levels produced by the IM regimen (total dose of 24 g up to 12 hours) were only very slightly lower than those produced by the IV regimen (total dose of 30 g over 12 hours). The only statistically significant difference between regimens, notably the fluctuation in levels, was predictable in that the difference between maximum and minimum serum levels could be expected to be greater with an IM than an IV regimen.

Sibai *et al.*[3] have compared an IV regimen using a maintenance infusion of 2 g/h with an IM regimen similar to Pritchard's in 15 patients with severe pre-eclampsia. They also showed the regimens to be clinically equivalent in the prevention of seizures. However, they reported greater differences between serum magnesium levels than were noted in the present study. They found that higher levels were produced by the IM regimen, particularly in the first 3 hours.

Comparison between Sibai *et al.*'s[3] and the present study in respect of levels produced by the IV regimens revealed very similar mean maintenance levels of approximately 1,68 - 2,10 mmol/l and 1,7 - 1,9 mmol/l respectively. It was not possible to compare peaks after the loading dose (which was only 4 g in that study) as sampling in the present study only began at 30 minutes.

In contrast to the similarity in IV findings, the average maintenance levels achieved with our IM regimen (1,5 - 1,8 mmol/l) were lower than those produced by Sibai *et al.*'s[3] IM regimen (1,9 - 2,7 mmol/l). Pritchard[6] has also reported higher levels (2 - 3,5 mmol/l) than ours, with an identical IM regimen.

Neither Sibai *et al.*[3] nor Pritchard[6] provide baseline serum magnesium levels for their patients. In the present study baseline levels were at the lower end of normal and perhaps this could account for the fact that similar regimens to those used by other workers resulted in lower levels.

This explanation would, however, not be consistent with the fact that levels produced by the IV regimens in Sibai *et al.*'s[3] and the present study were so similar. Dommisse[7] also produced levels similar to these with an IV regimen involving 2 g/h.

The difference in the levels produced by the IM regimens of Sibai *et al.*[3] and the present study is particularly marked between 0,5 and 2 hours during which time identical amounts of $MgSO_4$ — a loading dose of 14 g (4 g IV and 10 g IM) — would have been received. Sibai *et al.*'s[3] mean levels were approximately 2,8 mmol/l at 0,5 hours and approximately 2,7 mmol/l at 2 hours compared with mean levels in the present study of 1,9 mmol/l and 1,7 mmol/l respectively. Sibai *et al.*[3] suggest that their high levels with the IM regimen in the first 3 hours may be due to the high loading dose, and this does appear to be a logical explanation. Although similar high levels were probably produced in the present study in the first 30 minutes (and were not recorded as levels were not measured at this time) the reason why our levels fell so much quicker and eventually to lower levels than in Sibai *et al.*'s[3] study is unclear.

The optimal serum magnesium levels required for control of eclamptic seizures are unknown. Pritchard[6] indicated that the levels of 2 - 3,5 mmol/l produced by his regimen were satisfactory for preventing convulsions in patients with severe pre-eclampsia, and Hall[8] suggested levels of 3 - 4 mmol/l for optimal control. Sibai *et al.*[4] also noted in a series of 13 patients who had fits while receiving magnesium that 11 had levels below 2 mmol/l.

On the other hand, Cruikshank *et al.*[9] suggested that therapeutic levels of magnesium may be lower than those recommended by Pritchard. Flowers *et al.*[10] suggest that levels of 1,24 - 2,47 mmol/l are usually satisfactory.

The findings of the present study, in which none of the patients had fits despite levels which were mostly below 2 mmol/l, support the contention that optimal levels may be lower than generally believed. However a group of only 17 patients is probably too small to make such an assessment accurately.

In summary, the present study has shown that seizures were controlled in our severely pre-eclamptic patients at serum levels lower than those generally considered therapeutic. There was little to choose between the IM and IV regimens in that they provided similar levels and a comparable clinical outcome. While the IM regimen has the disadvantage of painful injections, it has the advantage of greater convenience and safety. In our setting, pumps for IV infusion are not readily available and, in addition, the nursing staff may be too busy to provide the continuous monitoring required. The IM route, where a dose will only be given once reflexes, respiration and urine output have been checked, is likely to be safer.

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Reflections on trauma and violence-related deaths in Soweto, July 1990 - June 1991

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This is a retrospective analysis of 5 600 deaths registered in Soweto from July 1990 to June 1991. The impact of trauma and violence on the overall mortality pattern was assessed. The majority of deaths occurred in people under the age of 50 years and more men died than women. In 40% of male deaths, the cause was stated as 'ill-defined' or 'unknown'; this was the case in an even higher percentage of female deaths (50,5%). Trauma or violence accounted for 28,5% of all deaths. The gender difference was particularly visible in the trauma category, viz. 89,5% and 10,5% in men and women respectively. Young men (20 - 29 years) were particularly affected by trauma and violence-related deaths (38,5%). The major types of injuries inflicted were gunshot wounds (33%), unspecified multiple injuries (32%) and stab wounds (27%). Motor vehicle accidents accounted for only 8% of deaths. The urgent need for intervention programmes to prevent unnecessary loss of life, targeted especially at young adults and children, is highlighted.

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Soweto (an acronym for South-Western Townships) was established in 1939 and is the largest black township in South Africa. It covers an area of approximately 660 hectares and is situated 15 km south-west of Johannesburg. Soweto's historical, geographical and demographic characteristics are probably similar to other rapidly expanding urban and peri-urban townships. Such rapid urbanisation has resulted in many public health problems.

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