Magnesium Sulphate Therapy in Women with Pre-Eclampsia and Eclampsia in Kuwait

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Key Words

Magnesium sulphate therapy · Pre-eclampsia · Eclampsia

Abstract

Objective: To evaluate the outcome of the use of MgSO₄ therapy in women with severe pre-eclampsia in Kuwait from January 2002 to December 2004. **Subjects and Methods:** The study involved 450 women managed at the Maternity Hospital in Kuwait with a blood pressure of 160/110 mm Hg and proteinuria of >0.3–5 g/24 h. A loading dose of 4 g MgSO₄ was administered intravenously over 20 min and then the maintenance dose continued at 1 g/h for 24 h postpartum. Magnesium sulphate toxicity was monitored by urine output, deep tendon reflexes and serum magnesium levels and managed with an infusion of 10 ml of 10% calcium gluconate and cessation of magnesium infusion. Adjunct therapy included intravenous hydralazine 10 mg and labetalol 100 mg. The mode of delivery was determined after stabilizing the patient. **Results:** The women included Kuwaitis (n = 200, 44.4%), Asians (n = 129, 28.7%) and other Arabs (n = 116, 25.8%) with a mean age of 29.7 ± 6.7 years (primigravida: n = 233, 51.8%; other parities: n = 217, 48.2%). Antenatal complications included intra-uterine growth restriction (n = 136, 30.2%), oliguria (n = 39, 8.7%), haemolysis, elevated liver enzymes and low platelet count syndrome (n = 30, 6.6%), abruptio placentae (n = 20, 4.4%), eclampsia (n = 15, 3.3%),

and preterm birth (n = 253, 55.2%). Caesarean section (n = 241, 53.6%) was the main mode of delivery. The perinatal mortality rate was 27 per 1,000. Magnesium sulphate toxicity observed as reduced tendon reflexes occurred in 14 (3.1%) patients and flushing, nausea and vomiting and blocked nostrils in 86 (19.1%). There was no association between adverse outcomes and maternal serum magnesium concentrations and no maternal mortality occurred. **Conclusion:** Magnesium sulphate was effective in preventing recurrence of eclamptic fits and safe for both mother and fetus.

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Introduction

Pre-eclampsia is a major complication of pregnancy, affecting 5–10% of all pregnancies. It is a disorder of the placenta with multisystem involvement that leads to severe maternal morbidity and mortality from associated renal, haematological, hepatic and cerebral impairment, with oliguria, haemolysis and eclamptic fits [1] and an exaggerated inflammatory response and inappropriate endothelial activation, and with microthrombus formation that further compromises blood flow to organs [2]. Eclampsia complicates 1 in 100–1,700 pregnancies in the developing countries and 1 in 2,000 pregnancies in the developed world, with more than 50,000 maternal deaths

worldwide each year, mostly in developing countries, and causes high perinatal mortality from intra-uterine growth restriction and iatrogenic preterm delivery in the interest of the mother and the fetus.

The prevention of eclamptic fits has been based on the perceived contemporaneous cause of the disorder [6]. Renal decapsulation, fluid drainage, implantation of ureters into the colon, mastectomy and oophorectomy were common modalities of treatment before the 18th century. Thereafter, stomach lavage, and high colonic flushings and phlebotomy were in vogue. Stroganoff introduced sedation with morphine sulphate and chloral hydrate in 1930 and various anticonvulsant drugs such as diazepam, phenytoin, chlormethiazole, barbiturates and lytic cocktail came into use, but with resultant severe side-effects and a high rate of recurrent eclamptic fits [7, 8]. In 1924, Lazard [9] successfully used magnesium sulphate to treat eclamptic seizures. Concerns about the potential side-effects and toxicity of magnesium sulphate and safety of the parturient and the fetus as well as a lack of understanding of the mechanism of action prevented its worldwide use.

There is currently a better understanding of the mechanisms of action of magnesium sulphate in regulating the neuromuscular excitability by acting directly on the myoneural function by antagonizing N-methyl-D-aspartate receptor activation [10–14]. Consequently, many studies have been carried out on the efficacy and safety of magnesium sulphate compared with placebo such as phenytoin and diazepam in the treatment of pre-eclampsia and eclampsia [15–17]. Recurrence of seizures has been found to be less common with magnesium sulphate therapy compared with phenytoin and diazepam, with a reduction in maternal mortality. With the worldwide menace of pre-eclampsia/eclampsia, a call for international action was therefore inevitable [18, 19]. The Magpie Trial Collaborative Group [5] was an elegant response to this call; in this study, involving 175 hospitals in 33 countries worldwide, 10,141 women with pre-eclampsia were enrolled. The study was stopped by the data monitoring board earlier than planned as results from the first 8,483 women showed such a strong benefit of magnesium sulphate with 58% less likely to progress to eclampsia and 45% less likely to die in childbirth compared with placebo-treated women, but there was no difference between the two groups in the risk of newborn deaths [5, 20]. In this account, we report the evaluation of the outcome of the use of $MgSO_4$ in the Maternity Hospital in Kuwait from January 1, 2002 to December 31, 2004. The study was approved by the Ethics Committee of the Hospital.

Subjects and Methods

Patients

This is a prospective descriptive study, involving 450 women admitted with severe pre-eclampsia or eclamptic fits, who received magnesium sulphate therapy and delivered at the Maternity Hospital during the study period. The Maternity Hospital is the biggest maternity unit in Kuwait and the obstetric and gynaecological teaching hospital of Kuwait University, catering for over 40% of deliveries in the country with an annual delivery rate of 14,000. Magnesium sulphate therapy to abort eclamptic fits and prevent recurrence was started at the hospital in 1998. In 2002, a database including all data connected with pre-eclampsia was started.

Inclusion criteria were: (1) severe pre-eclampsia: blood pressure $\geq 160/110$ mm Hg sustained 6 h apart, elevated blood pressure plus proteinuria 0.3–5 g/24 h, massive oedema, oliguria <500 ml, systemic symptoms like pulmonary oedema, headaches, diplopia, right upper quadrant pain, elevated liver enzymes or low platelet count; (2) eclampsia: verifiable history of fits at home, on the way to the hospital or inside the hospital, while all cases of epilepsy, encephalopathy, tetanus, meningitis, hypoglycaemia, keto-acidosis and pyrexia were excluded.

Clinical Examination of the Patients

On admission, each patient was subjected to clinical examination which included history of the present pregnancy and its management. The gestational age was usually calculated from the last normal menstrual period and confirmed by ultrasound at about 18–22 weeks of gestation. Relevant past obstetric, medical, surgical, drug, social and family histories were reviewed. Physical examination included general health of the patient, blood pressure estimation with Korotkoff phase 4 for the diastolic blood pressure, examination of the gravid uterus to exclude intra-uterine growth restriction, and fetal lie and presentation. Every patient had initial baseline investigations such as complete blood count for haemoglobin and haematocrit, white blood cells and platelets; renal function tests including electrolytes, urea, creatinine, and uric acid; liver function tests for elevated aspartate transaminase, alanine transaminase and lactate dehydrogenase; coagulation profile (elevated prothrombin time, partial thromboplastin time and fibrinogen degradation products), 24-hour urine for creatinine clearance and total amount of protein in the urine, and serum magnesium level.

Initial fetal examination and continuous fetal monitoring was carried out in each patient. If the patient was admitted with a history of previous eclamptic fits or had fulminating pre-eclampsia, she was immediately admitted to the intensive care unit and given magnesium sulphate intravenously.

Protocol for Administration of Magnesium Sulphate

The loading dose was 4 g i.v. over 20 min and then the maintenance dose continued at 1 g/h for at least 24 h after delivery. Magnesium sulphate therapy was aggressively monitored with urinary output (>120 ml in 4 h), deep tendon reflexes and serum magnesium levels.

Magnesium sulphate toxicity was indicated by loss of reflexes and drowsiness, poor urine output and high serum magnesium levels and treatment used included an antidote in the form of an infusion of 10 ml of 10% calcium gluconate; in addition, magnesium sulphate infusion would be stopped for 1–2 h.

Adjunct Therapy: Antihypertensive Therapy

The first-line therapy was with hydralazine 10 mg i.v. slowly, and a repeat dose of 5 mg i.v. after 20 min, and the second-line drug used was labetalol, starting with 50–100 mg i.v. slowly.

Timing of Delivery

All the 450 patients with pre-eclampsia, antenatal eclamptic fits, and other complications gave birth as soon as the fits and high blood pressure were controlled. The choice of the mode of delivery depended largely on the Bishop score: if it was favourable (i.e. ≥ 7), induction of labour was initiated; however, if the Bishop score was < 7 , immediate caesarean section was carried out; 351 women had induction of labour. Data about obstetric and neonatal outcome of the general maternity population during the study period were collected for comparison.

Statistical Analysis

Data were analysed with Statview software. Mean $\pm$ SD was calculated for paired values. Differences among groups were estimated by the Student *t* test. The Mann-Whitney test was used for data from unpaired groups of observations, and χ^2 statistics with Yates' correction, approximation of Katz and linear regression analysis were applied when appropriate. Significance was set at $p = 0.05$.

Results

Of the 33,162 total deliveries during the 3-year study period, 1,283 (3.9%) were complicated by pregnancy-induced hypertension defined as a blood pressure of 140/90 mm Hg starting after 20 weeks of gestation and persistent 6 h apart. Magnesium sulphate was administered to 450 (35.1%) women with severe pre-eclampsia and 15 (1.1%) who developed eclamptic fits out of the women with pregnancy-induced hypertension; 15 women out of the 450 (3.3%) with severe pre-eclampsia also developed eclampsia. The characteristics of the study patients compared with their counterparts in the maternity population are listed in table 1. Severe pre-eclampsia was significantly more common among non-Kuwaitis ($n = 250$, 55.6%) compared to Kuwaitis ($n = 200$, 44.4%; OR = 1.82, 95% CI 1.087–2.285, $p < 0.004$). Women in the age range of 31–40 years ($n = 208$, 46.3%) were more likely to have severe pre-eclampsia compared with younger and older counterparts (OR = 1.55, 95% CI 1.40–1.71, $p < 0.001$), especially in their first pregnancy. Primigravidity had an important association with pre-eclampsia (OR = 2.20, 95% CI 2.01–2.41, $p < 0.001$). Significantly more pre-eclamptic women delivered much earlier than the general population (35.4 vs. 38.9 weeks, $p < 0.05$), with 56.2 versus 7.8% having preterm delivery (below 30 weeks of gestation: OR = 6.11, 95% CI 4.56–8.19, $p < 0.001$; between 30 and 36 weeks of gestation: OR = 7.49, 95% CI 6.73–8.34, $p < 0.001$). As summarized in table 2, there were differential manifesta-

Table 1. Socio-demographic characteristics of the patients

	Pre-eclampsics	General maternity
Ethnicity		
Kuwaitis	200 (44.4)	17,576 (53)
Non-Kuwaitis	250 (55.6)	15,586 (47)
Asians	129 (28.7)	–
Non-Kuwaiti Arabs	116 (25.8)	–
Others	5 (1.1)	–
Age (mean $\pm$ SD), years	29.7 $\pm$ 6.7	29.4 $\pm$ 5.8
Age group		
≤ 20	30 (6.6)	2,951 (8.9)
21–30	212 (47.1)	22,770 (59.7)
31–40	208 (46.3)	9,915 (29.9)
> 40	–	497 (1.5)
Parity (mean $\pm$ SD)	1.24 $\pm$ 0.34	–
0	233 (51.7)	7,793 (23.5)
1–4	137 (41.1)	19,101 (57.6)
≥ 5	32 (7.2)	6,268 (18.9)
Gestation at delivery (mean $\pm$ SD), weeks	35.4 $\pm$ 3.8	38.9 $\pm$ 1.8
< 30	44 (9.8)	531 (1.6)
30–36	209 (46.4)	2,056 (6.2)
37–40	197 (43.8)	25,004 (75.4)
> 40	–	5,571 (16.8)

Figures in parentheses indicate percentages. 253 (56.2%) women had preterm delivery; 351 (78%) had induction of labour but 142 (40.6%) were delivered with caesarean section.

Table 2. Antenatal complications of pre-eclampsia on admission to the intensive care unit

	Patients
High blood pressure $\geq 160/110$ mm Hg	450 (100)
Proteinuria	450 (100)
Headaches	180 (40)
Epigastric pain	75 (16.7)
Blurred vision	62 (13.8)
IUGR	136 (30.2)
Oliguria	39 (8.7)
HELLP syndrome	30 (6.6)
Abruptio placentae	20 (4.4)
Eclampsia	10 (2.2)

Figures in parentheses indicate percentages. Other patients with eclampsia: 3 intrapartum and 2 postpartum.

IUGR = Intra-uterine growth restriction; HELLP = haemolysis, elevated liver enzymes, low platelet count.

Table 3. Outcome of magnesium sulphate therapy

Side-effects	
Toxicity with reduced tendon reflexes	14 (3.1)
Other features (flushing, nausea and vomiting, blocked nostrils and headaches)	86 (19.1)
Days of ICU stay	
≤2	316 (70.2)
3–4	97 (21.6)
5–6	23 (5.1)
>6	14 (3.1)
Postnatal complications (causes of long stay in the ICU ≥4 days)	
Persistent hypertension	47 (10.4)
Massive generalized oedema	32 (7.1)
Low platelet count (<50,000)	28 (6.2)
Wound haematoma	25 (5.5)
Infection (chest, UTI, wound)	19 (4.2)
Transient blindness	4 (0.8)
Disseminated intravascular coagulopathy	4 (0.8)
Recurrent seizures	1 (0.2)

Figures are numbers, with percentages in parentheses.
ICU = Intensive care unit; UTI = urinary tract infection.

tions of fulminating pre-eclampsia such as headaches, epigastric pain, and blurred vision. Intra-uterine growth restriction occurred in 136 (30.2%) of the women, while 39 (8.7%) had oliguria defined as urinary output of less than 25 ml/h. In 30 (6.6%) women, there was evidence of haemolysis, elevated aspartate and alanine transaminases and low platelet count (<50,000/dl).

Outcome of Magnesium Sulphate Therapy

As shown in table 3, magnesium sulphate toxicity manifested by reduced tendon reflexes was observed in 14 (3.1%) women. Two (0.4%) patients had eclamptic seizures while on MgSO₄ therapy. Other side-effects including flushing, nausea and vomiting and blocked nostrils were cumulatively demonstrated in 86 (19.1%) of the women; 316 (70.2%) stayed in the intensive care unit for less than 48 h, 413 (92%) for 4 days or less but 14 (3.1%) women for more than 6 days. The reasons for the prolonged stay in the intensive care unit included persistent hypertension, generalized oedema, and low platelet count resulting in wound haematoma. Four women had transient blindness. There was no maternal mortality.

Obstetric Outcome

Two hundred and forty women (53.6%) of the pre-eclamptic women were delivered by caesarean section

(OR = 2.71, 95% CI 2.48–2.96, $p < 0.001$). Assisted vaginal delivery with forceps/vacuum was also more common in pre-eclamptic women than women in the general maternity population without pre-eclampsia (OR = 1.90, 95% CI 1.39–2.62, $p < 0.01$). Significantly more pre-eclamptic women gave birth to babies with a birth weight of less than 1,000 g (OR = 7.32, 95% CI 5.05–10.60, $p < 0.001$) or below 2.5 kg (OR = 6.59, 95% CI 6.00–7.23, $p < 0.001$). Pre-eclampsia was more significantly associated with intra-uterine growth restriction than the general maternity population (OR = 4.82, 95% CI 4.28–5.46, $p < 0.01$): low Apgar score of 1–3 (OR = 3.64, 95% CI 3.26–4.28, $p < 0.001$) and Apgar score of 4–6 (OR = 3.84, 95% CI 3.34–3.98, $p < 0.01$).

Of the 15 women with eclamptic fits, 10 (66.7%) had them antenatally, 3 (20%) intrapartum and 2 (13.3%) postpartum including 1 (6.7%) with recurrent seizures. Their mean age was 24.8 ± 2.6 years (range 20–31), with an admission blood pressure of 130/80–200/120 mm Hg and proteinuria of 0.8 ± 0.4 g/day (range 0.3–5.0); gestation on admission and delivery was 35.2 ± 1.4 weeks (range 25–39 weeks of gestation). Most of the eclamptic women ($n = 9$, 75%) were delivered by caesarean section. The mean birth weight was 2.5 ± 0.4 kg (range 0.650–3.050 kg) and there was 1 intra-uterine fetal death and 1 early neonatal death from severe pre-eclampsia. Duration of stay in the intensive care unit was 2.4 ± 0.3 days mainly due to the need to complete magnesium sulphate therapy. The mean duration of hospitalization was 4.8 ± 0.8 days (range 4–6 days).

Magnesium sulphate toxicity was evaluated in 14 pre-eclamptics and 40 women on MgSO₄ without reduction of deep tendon reflexes (1.9 vs. 1.8 mM) and in 2 eclamptics with reduced tendon reflexes compared to 13 without (2.1 vs. 1.9 nM) while on MgSO₄ therapy. There were no significant differences between the groups in the serum Mg concentrations.

Discussion

Although 450 women treated with MgSO₄ had severe pre-eclampsia/eclampsia, there was neither life-threatening maternal morbidity nor mortality. Minor side-effects included flushing and signs of magnesium sulphate toxicity with recurrence. The safety of magnesium in this study was probably facilitated by limiting the loading dose of magnesium to 4 g and the maintenance dose to 1 g/h by intravenous route, as recommended by the Royal College of Obstetricians and Gynaecologists evidence-

based guidelines for the management of eclampsia [21]. Although the serum magnesium levels were essentially higher in those with reduced tendon reflexes, the difference did not reach the level of significance when compared with their counterparts without reduced tendon reflexes. Clinical assessment is therefore as important as serum magnesium sulphate levels for monitoring magnesium sulphate toxicity, as most serious complications of magnesium sulphate therapy are usually a result of human errors [22]. The findings of this study that only 2 (0.4%) women had eclamptic seizures while on MgSO₄ therapy and no maternal mortality confirm the report of the Eclampsia Collaborative Trial of 9,966 women from 33 countries that MgSO₄ therapy in eclampsia reduced maternal morbidity and deaths [23]. The present study also confirms the Cochrane review [24] of 6 clinical trials involving 11,444 women showing that magnesium sulphate more than halved the risk of eclampsia and maternal death [20].

Magnesium sulphate therapy in pre-eclampsia has not been associated with improved neonatal outcome in the short-term [5, 23–25]. There are many confounding factors that contribute to adverse neonatal outcome, and therefore make the evaluation of the neonatal outcome after magnesium sulphate therapy difficult, such as primigravidity (52%), preterm delivery in 56 and 53% of pre-eclamptic and eclamptic women, respectively, and intra-uterine growth restriction among 30.2% of the women in the present study. In the Magpie study [5], more than 53% of the babies were born underweight (less than 2.5 kg). One should, however, take into account that most cases of perinatal morbidity in pre-eclampsia usually occur very remote in time from the exposure to MgSO₄. Riaz et al. [26] evaluated the effects of maternal magnesium sulphate treatment on newborn infants delivered at ≥34 weeks of gestation whose mothers received a minimum of 12 h of intravenous MgSO₄, and beyond the immediate

postdelivery period, there were no additional complications in this cohort attributable to prenatal MgSO₄ exposure. This has recently been confirmed by the follow-up of 4,483 children of the Magpie Trial [27] at 18 months after exposure of their mothers to MgSO₄. There was no increased risk of death or disability.

Like the present study, two studies at the Rotunda Hospital in Dublin [28] and the Yorkshire region of the UK involving 16 maternity units using a common guideline of MgSO₄ therapy for pre-eclampsia for a 5-year prospective study [29] confirmed the outcome. There were no maternal deaths but about 72% of these women were delivered by lower segment caesarean section and the mean birth weight was 2.54 kg due to intra-uterine growth restriction and preterm delivery. In a recent economic evaluation of the Magpie trial by Simon et al. [30], MgSO₄ therapy for pre-eclampsia was found to cost less and prevent eclampsia, especially in low gross national income countries. Cost-effectiveness substantially improved if magnesium sulphate was used for severe pre-eclampsia. From the results of the present study and the foregoing review, there is compelling evidence of the safety and effectiveness of MgSO₄ therapy for pre-eclampsia/eclampsia.

Conclusion

Magnesium sulphate is safe for the mother and fetus, used as an anticonvulsant in severe pre-eclampsia and eclampsia reducing maternal morbidity and mortality and cost of care. The prevalence of magnesium sulphate toxicity was very mild. Monitoring is important in the protocol for magnesium sulphate therapy to diagnose toxicity early and to treat it using antidote calcium gluconate.

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