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ORIGINAL ARTICLE

A COMPARATIVE STUDY OF LOW DOSE MAGNESIUM SULPHATE REGIME VS STANDARD DOSE PRITCHARD REGIME IN THE MANAGEMENT OF ECLAMPSIA IN INDIAN SCENARIO

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ABSTRACT: OBJECTIVES: The aim of the study is to compare the Low dose magnesium sulphate regime Vs standard dose with regard to the efficacy, maternal outcome and fetal - neonatal outcome. **MATERIALS & METHODS:** The study was conducted at Govt. General Hospital Kakinada from June 2009 to September 2010. A Total of 100eclampsia patients were studied with50 cases in each group. In Low dose regime, a loading dose of 4gm Magnesium Sulphate (20ml of 20% solution) given slow IV over 20 minutes. This is compared to standard Pritchard regimen and a maintenance dose of 2gm deep IM 4th hourly up to 24hrs after delivery/ last convulsion whichever is later. **RESULTS:** Low dose magnesium sulphate regimen is as effective as Pritchard standard regimen in controlling eclamptic convulsions. No increase in maternal morbidity, mortality and no increase in perinatal morbidity, mortality were noted in the study group. **CONCLUSION:** A lower dose of magnesium sulphate is suitable and equally effective in Indian women who on an average weigh much less than the western counterparts to control convulsions in eclampsia with no increase in maternal mortality & morbidity (or) perinatal mortality & morbidity with the added benefit of reducing the side effects. The results obtained with this low dose regime bring out the focus for the need to review the correct dose of magnesium sulphate in Eclampsia in Indian scenario.

KEYWORDS: Eclampsia, low dose Mgso4 Regime.

INTRODUCTION: Eclampsia: Eclampsia is convulsions or coma in patients with Preeclampsia. Second most common cause of maternal mortality and morbidity in underprivileged population of India. Types: 1. Antepartum Eclampsia 2. Intrapartum Eclampsia 3. Postpartum Eclampsia Recent data reveal an increase in the proportion of women who develop Eclampsia beyond 48hrs after delivery.
Management includes Anticonvulsants, antihypertensives, fluid and electrolyte balance and termination of pregnancy.

Until recently the treatment of eclampsia varied throughout the world. Various drugs and regimens have been advocated for the management of eclampsia and imminent eclampsia. India made its contributions when Dr. krishna dutta[1]introduced famous lytic cocktail in 1950, In Dr. krishna menon's[1] regimen the drugs used were Pethidine, promethazine and chlorpromazine, reduced perinatal mortality upto certain extent, but it is inadequate to control convulsions and its recurrence. Lean regime in which Diazepam is used.

Of all the anticonvulsants used in last 50 yrs., only magnesium sulphate has retained its popularity, as reviewed by chesley[2](1978), that magnesium sulphate is effective in preventing convulsions in women with preeclampsia and in stopping them in those with eclampsia and also has some beneficial effects like vasodilatation, increased uterine and renal blood flow.

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The major breakthrough in the management of eclampsia came when Dr. J. A prichard[3] published his standard protocol in 1984.In many parts of the world, Pritchard regime consider standard, but it sometimes ends up with toxicity, due to its high dosage, because the women Pritchard studied obese and well-nourished from developed country, the same dosage may not apply to the lean and malnourished of developing countries like India.

Pritchard himself stated that "If a woman is known to be or appear to be small, the dose should probably be limited." - J. A. Pritchard, American Journal of Obst. & gyn vary according to the patient's weight or body mass index. "However this has never been adequately evaluated." - Andrea Witlin[4], Clinical Obst &Gyn.1999 - Winit Phuapradit et al - Bankok.- Asia- Oceania J. Obst & Gyn. 1993

In many parts of the world, Pritchard regime is considered standard, but it sometimes ends up with toxicity due to high dose. With this background low dose protocol has been formulated to suit our Indian women who weigh around 50-60kg at term the present study is undertaken to compare both the regimes in Indian population.

MATERIALS AND METHODS: The study was conducted at Govt. General Hospital, Kakinada from June 2009 to Sept 2010. A Total of 100 Eclampsia patients were studied with 50 cases in each group.

Inclusion Criteria: History of convulsions in hypertensive gravidae, Primi and multi gravidae, Antepartum, intrapartum and postpartum Eclampsia.

Exclusion Criteria: H/O epilepsy, hysteria or other causes of convulsions Inter current Eclampsia Presence of localizing cerebral signs like stroke prior treatment with Magnesium Sulfate loading dose or phenytoin, presence of maternal complications like Jaundice, Renal failure, Oliguria, Pulmonary edema, HELLP syndrome, Abruptio placenta, Disseminated Intravascular Coagulation, Heart disease, Severe anemia Contraindications for Magnesium Sulfate therapy. If there is recurrence of convulsion, an additional dose of 2 gms is given by IV and previous schedule is continued as before.

MANAGEMENT: The standard principles of management of eclampsia were followed. Following protocol was used in low dose magnesium regime in eclampsia; Written informed consent was obtained from the cases, who were included in the study. Loading dose of four grams of magnesium sulphate (20%solution) was given intravenously over five minutes time. Subsequently, magnesium sulphate maintenance dose of two grams (50%solution) was given deep intramuscularly in alternate buttock every four hour till 24 hours after delivery or after last convulsion after 30 minutes of initial intravenous loading dose, additional 2grams of 20%mgso4 solution was given intravenously.

If convulsions were not controlled after repeating such two additional doses, then the case was shifted to standard Pritchard regime and was labeled as failure of low dose regime. Efficacy of low dose mgso4 regime was assessed by control of convulsions with low dose protocol and by noting the total quantity of mgso4 required for control of convulsions. All cases were monitored for evidence of magnesium toxicity in the form of absence of deep tendon reflexes, respiratory depression and measurement of serum magnesium levels.

If any toxicity noted, next dose of Mgso4 was withheld and the toxicity is managed. High blood pressure was controlled with calcium channel blocker nifedipine. It was used orally in both groups.

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Mgso4 and Nifedipine are supplied free of cost for the patients. Except for the dosage of mgso4, the rest of management was similar in both groups. On admission, a brief history was taken from attendants and general examination was carried out.

Patients were kept in left lateral position, oral suction was done, airway patency maintained and oxygen inhalation given. Intravenous access was secured and blood taken for necessary investigations. Capsule Nifedipine 10mg(preferable orally)was given if systolic BP exceeded 160mm of Hg or diastolic BP exceeded 100mm of Hg. Prophylactic antibiotic. inj. Ampicillin 500mg IV tid was started.

After initial treatment detailed history, general examination, obstetric and neurological examination was carried out. Foley's catheterization was done to monitor urine output. Lactated ringer solution was given125ml/hr. Patients were monitored initially every 15 minutes and every hourly after stabilization with regard to general condition, pulse rate, respiratory rate, BP, heart and lungs, knee jerks, urine output, fetal heart rate. The following investigations were done: Hb%, Renal function tests, Liver function tests, Platelet count, Blood grouping and typing, Clotting time, Bleeding time, Fundoscopy, Urine for albumin and sugar and microscopy.

MONITORING DRUG TOXICITY: Complications of magnesium sulphate include loss of patellar reflexes, Respiratory depression, Muscular paralysis and respiratory arrest cardiac arrest.

Treatment: Injection calcium gluconate 1 gm 10ml of 10 % solution slow I.V along withholding further doses of magnesium sulphate usually reverses.

Clinical monitoring was done to assess the toxicity of Magnesium Sulfate, though ideal would be to monitor serum Magnesium levels. The next IM dose of Magnesium Sulfate was given only if the following criteria were met. Respiratory rate >12/ min, Urine output >100ml in the preceding 4hrs, Patellar reflexes are present.

RESULTS: Our institution, being a tertiary referral centre, there is a high turnover of eclampsia cases. From June 2009 to October 2010 a period of 17 months there were a total of 112 eclampsia cases, of these 12 were excluded as per the exclusion criteria. Since this is a preliminary study, patients with maternal complications at admission were excluded from the study. A total of 100 cases of eclampsia were selected and randomized to study (low dose regime 4gms of 20% Mgso4 IV as a loading dose and 2 gms IM every 4^{th} hourly as maintenance dose until 24 hrs. after delivery or last convulsion whichever is later) and control group (Pritchard regimen).

There were 50 patients in each group. Patients in each group had almost identical clinical parameters like age, parity, number and type of convulsions, edema and proteinuria. This has made statistical comparison easy. In the present study, we observed that the majority of cases belonging to rural area and were from middle or low socio economic group, with body weight much lower than women from higher socio economic group.

70% of women had body weight of 50 to 60 Kgs. time tested Pritchard Regime with its dose schedule was standardized for western women having total body mass index much higher than women from developing countries including India. In the present study we observed that eclamptic convulsions were controlled in 94% cases with total magnesium sulphate of less than 20 grams i.e., 54.5% less than used in Pritchard Regime.

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UNBOOKED	70%	82%
BOOKED	30%	18%
PRIMI	80%	76%
MULTI	20%	24%
RURAL	72%	68%
URBAN	18%	22%
TRIBAL	10%	10%
<20 YEARS	22%	8%
20-30 YEARS	76%	88%
>30 YEARS	2%	4%

Table 1: REGISTRATION STUDY GROUP (n=50) CONTROL GROUP (n=50)

p>0.005

Majority of the patients were primigravidae, both in control and study groups.

mm of Hg	STUDY GROUP (n=50)	CONTROL GROUP (n=50)
<109	0%	0%
110-139	18%	10%
140-179	72%	80%
DBP <89	12%	8%
DBP 90-109	60%	48%
DBP 110-129	28%	32%
DBP >130	2%	4%

Table 2: SYSTOLIC and DIASTOLIC B. P. AT THE TIME OF ADMISSION

Clinical parameters which were required to be monitored in standard dose regimen were monitored in both groups. There was no significant difference in respiratory rate, urine out-put or presence of knee jerks in either of the groups. The decreased urine out- put found in both cases and controls responded to simple fluid challenge.

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STUDY GROUP (n=50)	CONTROL GROUP (n=50)	
ANTEPARTUM	68%	84%
INTRAPARTUM POSTPARTUM	14% 18%	10% 6%
GESTATIONAL AGE <28 wks	8%	2%
29-32wks	6%	14%
33-36 wks	18%	10%
>36 wks	50%	62%

Table 3

	STUDY GROUP	CONTROL GROUP
RECURRENCE OF CONVULSIONS SPONTANEOUS VAGINAL DELIVERY ASST. VAGINAL DELIVERY LSCS	6% 78% 10% 12%	4% p>0.005 70% p>0.005 8% p>0.005 22 p>0.005
MATERNAL COMPLICATIONS MEAN PATIENT WEIGHT(KG)	2% 56.3	12% p>0.005 57.3 p>0.005
PERINATAL COMPLICATIONS	36%	28% p>0.005

TABLE 4: RECURRANCE, MODE OF DELIVERY AND OUTCOME

Instance of recurrent convulsions 4% in control group and 6% in study group seen with no residual neurological effects in any case. All recurrence occurred less than 13 hours from the loading dose. All recurrent convulsions in study group were controllable with bolus dose of magnesium sulphate. However, 1 case from control group required midazolam to control convulsion. Blood pressure at recurrence was high in only two patients in study group though all were on ante hypertensive medication.

First convulsion to delivery interval was similar in both groups with delivery not being delayed in any case. Gestational age, mode of delivery, method of induction and indications for LSCS were similar in both groups. The main gestational age was 35 plus or minus 2.54% vs. 34.3% plus or minus 3.5% weeks in our study. In our study 68% of study group in 70% of controlled group required induction of labor.

Cesarean section rate was 6% in study group and 12% in controlled group. Maternal complications like PPH is 2% in study group and 12% in controlled group, there were no maternal

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deaths in both groups. The better maternal mortality and morbidity in our case is due to selection where eclampsia patients with maternal complications at admission were excluded.

Live birth rate was 84% in study group and 80% in control group. Neo natal deaths 14% in study and 18% in control groups. PNMR in our study is 20%. Prematurity, placental abruption and growth restriction were common causes for perinatal deaths.

TABLE 5: FETAL OUTCOME.

FETAL OUTCOME

	STUDY GROUP	CONTROL GROUP
FETAL OUTCOME		
PRETERM NONVIABLE	1(2%)	2(4%)
IUD	2(4%)	2(4%)
STILL BIRTHS	6(12%)	9(18%)
LIVE BIRTHS	41(82%)	37(74%)
BIRTH WEIGHT		
BRITH WT	(n=43+1)	(n=45)
<1.5 KG	11(25%)	15(33.33%)
1.6-2KG	10(22.72%)	8(17.77%)
2.1-2.5 KG	17(38.63%)	14(31.11%)
2.6-3 KG	4(9.09%)	7(15.55%)
>3 KG	2(4.54%)	1(2.22%)
APGAR SCORE		
APGAR	(n=34+1)	(n=32)
<3	4(11.42%)	3(9.37%)
4-7	10(28.57%)	15(46.87%)
>8	21(60%)	14(43.75%)

It was observed that there is a trend for better apgar scores in study than in control groups. 60% of our study group and 58% of control group has apgar more than 8 at 1 minute. Despite the overall fetal outcome in terms of NICU admissions (32% vs. 44%) NICU stay (10% vs.12%) less than 2 days and neo natal deaths (14% vs. 18%) were similar in both groups.

Time	Cases (n=50)	Percentage (%)
Control of convulsions with low dose regime	47	94%
Cases requiring additional IV bolus dose	02	04%
Cases requiring shift to Standard Pritchard regime and other anticonvulsants	01	02%

TABLE 6: Efficacy of low dose Magnesium Sulfate regime in controlling convulsions

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In our study, there was no significant difference in outcome of patients in both groups in terms of clinical parameters for monitoring, incidence of recurrence of convulsions, maternal, labor or perinatal outcome when high dose therapy has no positive contribution to outcome in eclampsia cases. It may safely be avoided.

DISCUSSION: Since the introduction of Pritchard regimen there has been a constant discussion regarding the dose of magnesium sulphate. Pritchard regime is a near ideal regime till the present day, at least in terms of control of convulsions, the need for monitoring and chances of toxicity always remain a problem. Hence a search for a simple regime which would have equal efficacy, less chance of toxicity and easy to monitor.

Many other workers have proposed various regimes for administration of magnesium sulphate as anticonvulsant in eclampsia. Zuspan FP[5] and Baba Sibai[6] both have proposed a protocol which consist of continuous I.V infusion of mgso4.Cruikshank[7]also modified the dose ofmgso4. A modified low dose regime has been proposed by Begum[8]Ret et al from Dhaka and sardesai suman[9] et al and found to be very effective and safe.

Eclampsia, though on the decline is still a major obstetric problem today. In spite of good antenatal care the developed nations are not yet able to prevent it completely. Though Pritchard's regimen is a near ideal regimen till the present day, at least in terms of control of convulsions, the need for monitoring and chances of toxicity always remain a problem. Hence a search for simpler regimen, which would have equal efficacy, less chances of toxicity and easy to monitor.

Our institution, being a tertiary referral centre, there is a high turnover of eclampsia cases. From June 2009 to October 2010 a period of 17 months there were a total of 112 eclampsia cases, of these 12 were excluded as per the exclusion criteria. Since this is a preliminary study, patients with maternal complications at admission were excluded from the study.80% cases had less than 3 convulsions before admission to hospital.

In 94%cases, low dose magnesium sulphate regimen was enough to control eclamptic convulsions. In the present study we also observed that the total dose of magnesium sulphate required for control of convulsions was less than 20gms that is 54.5%less than that is required in standard Pritchard regime.

There is no significant difference in knee jerks, urine output and respiratory rate In both groups. Control of blood pressure was similar in both groups. Combination of magnesium sulphate and nifedipine did not result in fall of blood pressure in any case. Carry home baby rate was 70% and 64%in study and control groups.

Both low dose and standard dose regimens are equally effective in controlling convulsions with success rate of 94%study group, 96%control group and recurrent convulsion rate in study group 6%and 4% in control group.

The surprising findings were that Pritchard's Regime the serum magnesium levels were not high as it was expected in women with low weight. They were in the range of 4 to 8 mg/ dl. In the magnesium sulfate metabolism 50% of the infused dose is excreted in urine when the concentration of magnesium exceeds 2 mg/ dl. Thus, even if we give Pritchard's Regime, the excess of magnesium is excreted by the kidneys.

The question is then why give handful salt, when you can get away with a pinch of salt. This is a strong justification for giving low dose regime. The rationale behind our study lies in the fact that

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Mg SO4 is not an innocuous drug though it would be ideal to monitor serum magnesium levels for patients on magnesium sulphate, it is not feasible in developing countries, thus, intense clinical monitoring is resorted to which may not always be possible in hospitals with high turnover and inadequate staff. Inadequate monitoring makes the women more susceptible to toxic effects as there is a narrow margin between therapeutic use and toxic levels.

Serum magnesium levels are 4 to 7 meq/ per liter is considered to be therapeutic. Loss of patellar reflex occurs at serum levels of 10 meq/ per liter. Serum levels above 10 meq per litre causes respiratory depression and that above 12 causes respiratory paralysis. Thus, there is a safety margin between 7 and 10 meq/ per liter during which loss patellar reflex occurs, providing a warning signal that the safe therapeutic level is crossed and serum level is fast approaching toxic levels.

The highest reported serum level achieved with low dose of 14 grams of magnesium sulphate even in patients with renal failure is well within therapeutic range and never enters the toxic range. As high doses are withheld in low dose regimen, there is no risk of w woman developing toxic side effect of magnesium sulphate. The main aim of giving high dose is to prevent further convulsions, which is expected to improve outcome.

When the recurrence rate does not vary irrespective of whether high dose is given or not, it may be safety avoided. The incidence of recurrent convulsions in our study, both in study and control group was well within the range quoted by collaborative eclampsia trial and also in Pritchard and Sibai's series. The low dose regimen requires less monitoring with less risk of toxicity, reduces the high dose painful intramuscular injections and its complications, improves patient compliance and reduces the overall cost of the therapy. This would be a welcome change in the developing countries where there are fewer qualified people available care to the large number of eclampsia patients.

CONCLUSION: Our study concludes that Low dose of Magnesium Sulfate is as effective as Standard Pritchard regime in the control and prevention of recurrent convulsions. Dose required for control of convulsion with low dose Magnesium Sulfate is less than half that of Pritchard regime. Low dose Magnesium Sulfate is sufficient to prevent recurrence in 94% of cases. Low dose regime requires less monitoring with no complications.

There was no Magnesium Sulfate related toxicity on clinical monitoring with low dose regime. In developing countries like India, it is not possible to treat all women with eclampsia in tertiary referral centres and majority of tertiary referral centres there is resource constraints. In such situations Low dose can be administered at PHCs and rural set-ups before transfer to higher centers, as it is safe and effective.

Low dose is simple to administer, easy to monitor and equally as effective as standard regime with comparable maternal outcome and perinatal outcome. low dose reduces the high dose painful intra muscular injection and its complications, improves patient compliance and reduces overall cost of therapy.

The results of present comparative study of both regimes confirm that the low dose is adequate for Indian women who weigh less than the western counter parts. Low dose magnesium sulphate was very effective as seizure prophylaxis in imminent eclampsia i.e., severe pre eclampsia with headache, vomiting or albuminuria[10]. In years to come, it will be an established protocol in India and will be a major stepping stone towards safe motherhood.

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