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ORIGINAL ARTICLE

A DOUBLE BLIND RANDOMIZED CLINICAL TRIAL COMPARING PRITCHARD'S REGIMEN WITH LOW DOSE REGIMEN IN WOMEN WITH SEVERE PRE ECLAMPSIA AND ECLAMPSIA

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ABSTRACT: OBJECTIVES: To compare Pritchard's regimen of magnesium sulphate with a low dose magnesium sulphate regimen in women with severe pre eclampsia and eclampsia. **AIMS**: 1.To determine if clinical signs and symptoms of magnesium toxicity are less in women with low dose as compared to Pritchard's regimen. 2. To determine if low dose magsulf will suffice in preventing onset of convulsions in severe pre eclampsia and recurrence of convulsions in patients with eclampsia. **MATERIALS AND METHODS: SETTING**: tertiary level teaching hospital in Tamilnadu, India. **PARTICIPANTS**: all women with eclampsia 1. All women with severe pre eclampsia meeting any of the following criteria: a) diastolic BP> 110 and proteinuria 2+ or more b) diastolic BP< 110 but 3+ proteinuria c) pre eclampsia with symptoms of impending eclampsia – headache, blurring of vision, epigastric pain. **RESULTS:** Primary outcome of side effects was not different in Pritchard's and low dose regimen. Secondary outcome of efficacy of low dose where low dose regimen was found to be equally efficacious to Pritchard's regimen in preventing recurrence of convulsions in eclampsia. **CONCLUSIONS:** 1. Magnesium sulphate is an effective and safe anti convulsant with very infrequent serious toxicity. Side effects with low dose regimen were not significantly less than those with Pritchard's regimen. 2. Low dose of magnesium sulphate can effectively prevent onset or recurrence of convulsions in women with severe pre eclampsia and eclampsia. 3. Implications for future research would be to test the minimum effective dose of magsulf and if only the loading dose is enough.
KEYWORDS: Magnesium sulphate, eclampsia.

INTRODUCTION: Severe pre eclampsia and eclampsia remain serious complications of pregnancy and are an important cause of mortality and significant morbidity in our country.[1,2]

The principles of management of this condition include control of blood pressure with anti-hypertensive, control of convulsions, monitoring for complications and initiation of steps for delivery of the foetus.[3,7] Measures to bring down the blood pressure are usually parenteral labetolol or hydrallazine or oral nifedipine.

The optimal anti convulsant for the management of severe pre eclampsia and eclampsia was disputed, till the Eclampsia Collaborative Group published its results in 1995, showing clearly that magnesium sulphate was more efficacious than phenytoin or diazepam.[4]

Not only does it diminish the risk of further convulsions but it also decreases maternal and neonatal morbidity.

However, in many primary health centers and in the peripheral hospitals magnesium sulphate has still not gained popularity. There is a fear of the rare, but sometimes fatal toxicity of respiratory arrest.

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The MAGPIE Trial collaboration group published their results in June 2002, where they reported that 25% of their patients experienced side effects of magnesium sulphate as compared to 5% in the placebo arm [5]. The side effects noted were mainly flushing, nausea or vomiting, respiratory depression, muscle weakness, thirst, dizziness, headache and absent deep tendon reflexes.

At around the same time that the Eclampsia Trial was being conducted, a much smaller study in Dhaka proved that magnesium sulphate was the optimal anti convulsant for eclamptics. However in view of the smaller size of Bangladeshi women and concerns about magnesium sulphate toxicity, a lower dose of magnesium sulphate was used.

The results of this low dose of magnesium sulphate in terms of preventing recurrence of convulsions were comparable to the standard regimen. In 1998, another study conducted in Dhaka[6] recruited 65 eclamptics to receive the "low dose" magnesium sulphate. Only one had a recurrent convulsion. None of the patients had respiratory depression, none required calcium gluconate, and all the patients maintained adequate urine output sufficient to continue magnesium sulphate. Serum magnesium levels were monitored and ranged between 1.74 – 6.0 mg/dL. Five patients had absent knee jerks. The patients with absent knee jerks also were found to have serum magnesium levels within the therapeutic range.

The low dose magnesium sulphate appears to control and prevent convulsions effectively. The profile of clinical side effects seemed to be less with low dose regimen than the Pritchard regimen. To determine whether the low dose regimen of magnesium sulphate has less side effects while at the same time being equally effective as the Pritchard regimen, a randomized clinical trial was carried out.

MATERIALS AND METHODS:

Setting: A tertiary level teaching hospital in Tamilnadu, India.

Participants:

1. All women with eclampsia.
2. All women with severe pre eclampsia meeting any of the following criteria.
    a) Diastolic BP > 110mm Hg and proteinuria of 2+ or more
    b) Diastolic BP < 110 mm Hg but 3+ proteinuria or more.
    c) Pre eclampsia with symptoms of impending eclampsia namely headache, blurring of vision, epigastric pain.

Design: A randomized open clinical trial. Randomization was done in blocks of ten using Clinstat computer programme. The drugs including the loading dose and the maintenance dose for each patient were packed in separate boxes and labeled serially from 1 to 200. The investigator was blinded to the identity of the contents of each box. (Either Pritchard's or low dose)Each patient received either a total dose of 45 gm (Pritchard's regimen), or 25 gm (low dose regimen) of magnesium sulphate over 24 hours.

The Pritchard's regimen of Magnesium Sulphate: The loading dose is 14gm of magnesium sulphate, of which 4gm of 20% magnesium sulphate is administered intravenously while 5gm of 50% solution PLUS 1ml of 2% xylocaine administered intramuscularly into each buttock. This is followed y 5gm of 50% solution intramuscularly 4th hourly for 24 hours.

OR

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The low dose Regimen: Here the loading dose is 10 gm of which 4 gm of 20% solution is administered intravenously and 3gm of 50% solution PLUS 1ml of 2% xylocaine administered intramuscularly, into each buttock followed by 2.5gm of 50% solution 4th hourly for 24 hours.

Treatment of recurrent Convulsions: In case of recurrence of convulsions after trial entry, 2 gm of magnesium sulphate would be administered slowly intravenously.

Anti hypertensives in Labour: If the woman was on anti hypertensives antenatally, the same was continued in labour. If the diastolic BP in labour was greater than 100mg Hg, cap nifedipine was given up to 10mg 6th hourly.

Monitoring in Labour: Hourly monitoring of pulse rate, BP, deep tendon reflexes, respiratory rate and urine output was made and side effects or evidence of toxicity if any were documented. Uterine contractions and progress of labour were monitored using partogram. The foetal heart rate was monitored by intermittent auscultation or electronic foetal monitoring. The decision regarding optimal mode of termination of pregnancy was made by the consultant of the respective unit.

Primary Outcomes: They were clinical toxicity profile/ side effects of magnesium sulphate in the different regimens namely the low dose regimen and the Pritchard regimen.

Side Effects:

1. Flushing, feeling of warmth, nausea or vomiting.
2. Headache, thirst, dizziness, muscle weakness.
3. Induration at site of injection.

Toxicity: Absence of tendon reflexes, respiratory depression.

Secondary Outcomes:

1. Recurrence of convulsions in cases of eclampsia.
2. Occurrence of convulsions in severe pre eclampsia.

Determination of sample Size: The MAGPIE trial collaboration group reported that the adverse effect in high dose magnesium sulphate regimen was 25%. In the Dhaka study, adverse effects were in nearly 10% with the low dose regimen. In order to show this magnitude of difference in adverse effects with 95% confidence interval and 80% power, the sample size required in each group was 100 women.

RESULTS:

Socio demographic characteristics of the recruited Patients: The mean age in Pritchard regimen arm was 23.19 ± 4.07 years and in low dose regimen arm was 24.27± 5.13 years. 26 patients in the former group were booked in our hospital as opposed to 30 in the second group (both these comparisons were not statistically significant).

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Number of previous Pregnancies (Fig. 1)

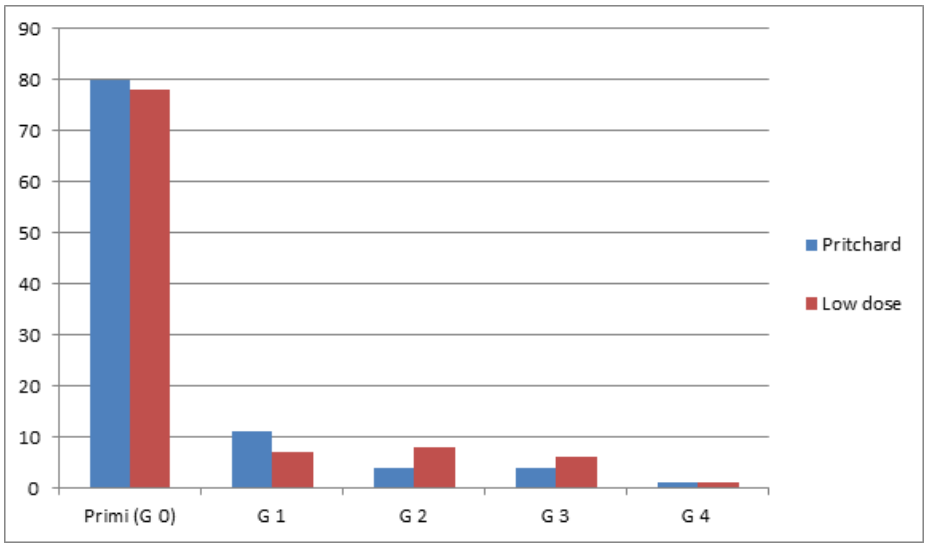

Fig. 1

In both the arms, women allocated were balanced with respect to age, booking, obstetric score, educational status and religion. Primis constituted 79% of patients recruited. 28% of patients were booked with us.

Which antihypertensive was used: (Fig. 2)

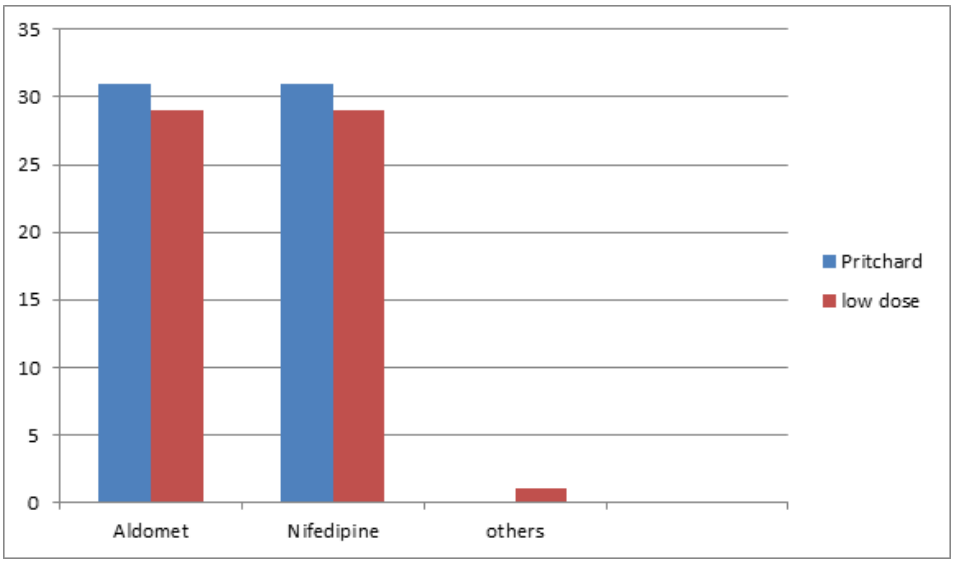

Fig. 2

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Number of eclampsia cases: (Fig. 3): Totally 39 eclamptics, of which 19 were in Pritchard regime arm, 20 in the low dose regime arm.

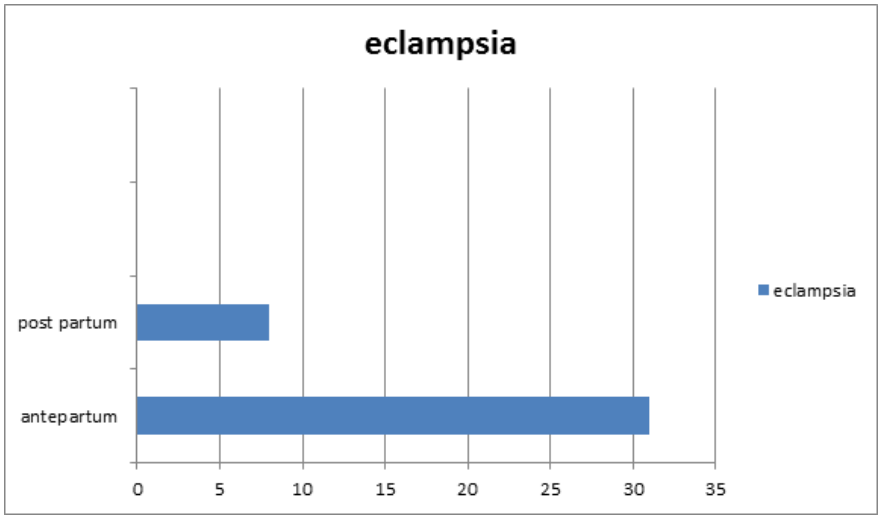

Fig. 3

Comparison of Outcome:

Side effects	Pritchard n=100	Low dose n=100	p value
Flushing	76/92	66/88	Ns
Nausea or vomiting	21/92	23/88	Ns
Respiratory depression	0/100	0/100	ns
Muscle weakness	5/92	7/88	Ns
Thirst	34/92	31/88	Ns
Headache	6/92	8/88	Ns
Dizziness	8/92	9/88	Ns
Drowsiness/confusion	15/92	14/88	Ns
Palpitation	7/92	8/88	Ns
Tingling/itching	4/92	4/88	Ns
Pain, burning	64/92	71/88	Ns
Induration	48/100	44/100	Ns
Abscess formation	0/100	0/100	Ns

Table 1: Primary outcome

ns: Not significant (p value > 0.05)

All patients could not be studied for side effects, because 20 patients (8 allocated to Pritchard regime and 12 allocated to low dose regime) had low Glasgow Coma Scale scores and could not respond to queries about the symptoms. Flushing was the most common side effect. Respiratory depression (resp rate< 16/min) did not occur in any of the 200 patients. 67.5% patients complained of pain at the site of injection. 46% had induration but none had abscess formation.

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	Pritchard n=100	Low dose n=100	p value
Number of eclamptics who had recurrent convulsion on magnesium sulphate	**1**	**2**	**Ns**
Additional magnesium sulphate given	**2gm**	**4gm**	**Ns**
No. of episodes of recurrent convulsions on magnesium sulphate	**1**	**1**	**Ns**

Table 2: Secondary Outcome

All the 3 women developed only one episode of recurrent convulsion, which was controlled with an additional 2 gm of magnesium sulphate.

Reasons for withholding magsulf	Pritchard n=100	Low dose n=100	p value
1. oliguria	10	14	Ns
2. respiratory depression	0	0	Ns
3. absent tendon reflexes	12	12	Ns
4. B.P. normalized	1	0	Ns
5. breakage of ampoules	2	1	Ns
6. cortical venous thrombosis	0	1	Ns

Table 3: Reasons for withholding magnesium sulphate

ns: Not significant (value > 0.05)

Absent tendon reflexes and oliguria (defined as urine output < 100 ml in 4 hours) were the most common reasons for withholding magsulf.

No. of patients on magnesium sulphate	Pritchard n=100	Low dose n=100	p value
1. admitted to ICU	4	8	Ns
2. ventilated	3	7	Ns
3. given calcium gluconate	0	0	Ns
4. HELLP syndrome	2	0	Ns
5. renal failure	1	1	Ns
6. cortical venous thrombosis	1	0	Ns
7. PPH requiring transfusion	1	0	Ns

Table 4: Serious maternal morbidity associated with magsulf

ns: Not significant (value > 0.05%)

Patients who were ventilated and most of those who required ICU care were those who were administered general anaesthesia for Caesarean section (because of low platelet counts, regional anaesthesia could not be administered). These women were not extubated immediately after surgery.

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	Pritchard n=96	Low dose n=96	p value
1. labour induced	65	60	Ns
2. vaginal delivery	55	50	Ns
3. No. of caesarean sections	41	46	Ns
4. Manual removal of placenta	1	2	Ns

Table 5: Labour and delivery

Most women in whom labour was induced delivered vaginally in both arms. 8 women had post-partum eclampsia - 4 in each arm and hence, labour and delivery outcomes were not analyzed in them. The number of patients who had manual removal of placenta was comparable in both groups.

DISCUSSION: There is ample evidence now that magnesium sulphate is the anti convulsant of choice, in women with severe pre eclampsia to prevent the onset of eclampsia, and to reduce the number of seizures in patients of eclampsia.

Magnesium sulphate even today is used with some reluctance because of the fear of magnesium toxicity, in the form of occasionally fatal respiratory depression in women who are much smaller than American women, and where monitoring of serum magnesium levels is difficult.

This study was conducted to see if a lower dose of magnesium sulphate will suffice in our women in reducing the occurrence or recurrence of convulsions, and to see if the side effects with magnesium sulphate was less in the low dose regimen.

The study was a randomized double blind clinical trial conducted in a tertiary center where 200 women with severe pre eclampsia and eclampsia were randomized to receive either Pritchard's regimen or low dose regimen of magnesium sulphate. The randomization was done in blocks of ten using computer generated numbers. The researcher, the patient and the medical personnel administering the drug and assessing the side effects were blinded to the contents of the pack (either Pritchard's or low dose regimen).

In the comparison of Pritchard's regimen versus low dose regimen, the groups generated by randomization were well balanced. At trial entry, 80% of the women were in their first pregnancy, only 25% of the patients had at least one antenatal visit with us. They were well matched with respect to mean age, religion and educational status.

The primary outcomes analyzed revealed that 82.6% and 75% of patients administered Pritchard's or low dose magnesium sulphate respectively had unpleasant side effects, of which flushing and thirst were the commonest side effects. This is in contrast to findings of the MAGPIE trial, which showed that 25% of patients experienced side effects as compared to 5% in the placebo arm.

Women allocated to low dose regimen experienced a side effect profile very similar to women allocated to the standard Pritchard's regimen. But none of the women recruited developed respiratory depression in both the arms, showing that serious toxicity of magnesium sulphate is indeed very rare.

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As the maintenance dose of magnesium sulphate was administered intra muscularly, pain and induration at the injection site was noted but none of the patients had injection abscess (which was reported in the Collaborative Eclampsia trial). Some women, 8 allocated to the pritchard's regimen and 12 allocated to the low dose regimen, could not be assessed for side effects as they had very low Glasgow Coma Scale scores.

Only three eclamptic patients had recurrence of convulsions: 2 allocated to low dose regimen and one allocated to Pritchard's regimen: the difference was not statistically significant. The rate of recurrent convulsions was not more in the low dose regimen; hence in this study low dose was equally efficacious in preventing recurrence of convulsions.

All the 3 women with recurrent seizures on magnesium sulphate had only one convulsion, which was controlled with 2 gm of magnesium sulphate administered slowly intravenously. None of the women with severe pre eclampsia, or the women with imminent symptoms developed seizures.

Magsulf was withheld, or one or more doses skipped in almost one-fourth of women allocated to both regimens, the commonest reasons being oliguria and absent tendon reflexes. None had respiratory depression since strict clinical criteria for withholding magsulf were used. Hence none required calcium gluconate.

Almost 85% of patients who had labour induced, delivered vaginally. The number of patients who had manual removal of placenta was 1% and 2% in Pritchard regimen and low dose regimen respectively. Hence the tocolytic effect of magsulf was not apparent, nor was it different in the two dosage regimens. The Caesarean section rate in the women recruited was 45.3%, but the commonest indication was foetal distress. The number of stillbirths in each arm was 14 and 13 respectively. Most stillbirths occurred in foetuses that were considered to be non-salvageable in our hospital (< 1 kg) and were administered misoprostol (PG E_1) for termination.

The sample size in this study may have been insufficient to detect minor differences which exist between the two dosage regimens in terms of incidence of side effects or recurrence of convulsions. But these minor differences may not have any clinical implications.

The incidence of recurrent convulsions in our eclamptic patients was comparable in both dosage regimens. From this study, low dosage regimen may suffice in our patients, but the sample size may be too small to bring out minor differences.

If a lower dose of magnesium sulphate which is about half the dose used in the standard Pritchard's regimen will suffice, researchers in Bangladesh have gone one step further to see if only a loading dose of magnesium sulphate will suffice in women with eclampsia. This needs to be evaluated further.

If a meta-analysis or studies with large number of women can confirm the efficacy of the low dose regimen or only the loading dose of magnesium sulphate in treatment of eclampsia, the clinical implications could be very significant. Magnesium sulphate can then be administered as a loading dose in many peripheral hospitals without a need to monitor signs of magnesium toxicity. Even in large centers, just the loading dose may suffice for patients who are delivered soon after admission.

CONCLUSIONS:

1. Magnesium sulphate is an effective and safe anti consultant with very infrequent serious toxicity. The side effects with low dose regimen were not significantly less than those with Pritchard's regimen.

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2. Low dose regimen of magnesium sulphate can effectively prevent onset or recurrence of convulsions in women with severe preeclampsia and eclampsia.
3. Implications for future research would be to test what the minimum effective dose of magnesium sulphate would be, and if only the loading dose of magnesium sulphate can have therapeutic effect.

BIBLIOGRAPHY:

1. WHO, UNICEF Revised 1990 estimates of maternal mortality. WHO/ FRH/ MSM/ 96 Geneva: WHO 1996.
2. Duley L. Maternal mortality associated with hypertensive disorders of pregnancy in Africa, Asia, Latin America and the Caribbean. Br J Obstet Gynaecol 1992; 99: 547-53.
3. Pritchard JA, Cunningham FG, Pritchard S. The Parkland Memorial Hospital protocol for treatment of eclampsia: evaluation of 245 cases. Am J Obstet Gynecol. 1984; 148: 951-63.
4. The Eclampsia Trial Collaborative Group. Which anti convulsant for women with eclampsia? Evidence from the Collaborative Trial. Lancet 1995; 345: 1455-63.
5. Do women with pre eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomized placebo controlled trial. Lancet 2002; 359: 1877-90.
6. Rashida Begum, Anowara Begum, Richard Johanson et al. A low dose (Dhaka) magnesium sulphate regime for eclampsia. Acta obstet Gynecol 2001; 80: 998-1002.
7. Pritchard JA. The use of magnesium sulphate in pre eclampsia – eclampsia. J Reprod Med 1979; 23: 107-114.

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