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STUDY AND COMPARE THE EFFECT OF LOW DOSE VERSUS STANDARD PRITCHARD REGIMEN OF MAGNESIUM SULPHATE ON MATERNAL AND PERINATAL OUTCOME IN ANTEPARTUM GROUP OF ECLAMPSIA: A RCT

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ABSTRACT

Background- Eclampsia is a well-known complication of hypertensive disorders in pregnancy. It's a common cause of maternal death in countries like India. Magnesium sulphate is the anticonvulsant of choice and can be administered by either intramuscular or intravenous route. The Pritchard regimen has been formulated as per women of western countries for intramuscular administration.. The Indian women on the contrary have low BMI & hence are at a greater risk of toxicity of magnesium sulphate **Methodology-** The study was conducted at a tertiary care hospital from October 2015 to September 2016 in Purulia on 86 eclamptic mothers who were randomized into two groups. Group 'A'(low dose group: A loading dose of 3gm of magnesium sulphate intravenously plus 5 gm intramuscularly 2.5 gm in each buttock followed by maintenance dose of 5gm i.m. [2. 5 gm i.m. alternate buttock] every four hours) or Group' B'(standard Pritchard regimen: loading dose of 4gm iv plus 10 gm i.m [5 gm.in each buttock] followed by maintenance dose of 10gm i.m [5 gm in alternate buttock] for every four hours .Toxicity was monitored clinically before administering maintenance dose of Magnesium Sulphate. Data was analyzed and entered in Microsoft Excel. **Results-** 90% of patients were primigravidas in low dose group and 83.72% patients in standard dose group..80.23 % had 1 to 3 convulsions. Recurrence of convulsion the primary outcome of our study was observed in 4.65% in low dose group as compared to 6.98% in standard Pritchard regimen group. Perinatal mortality was 25.58 % in the low dose group and 34.88% in the standard dose group. **Conclusion-** Low dose regimen has comparable efficacy in convulsion control in women with eclampsia.

KEYWORDS : Magnesium Sulphate, Pritchard Regimen, Eclampsia, Perinatal, Maternal, Low Dose Regimen

INTRODUCTION

Eclampsia is defined as the occurrence of one or more convulsions associated with the syndrome of pre-eclampsia.[1] Although the etiology of pre-eclampsia remains elusive, it is clinically characterized by the development of hypertension to the extent of 140/90 or more with or without edema, associated with proteinuria (0.3 gm. in 24 hours) after the 20 the week of pregnancy in a previously normotensive, non-protein uric women.[2] From the analysis of facts and figures, it was found that maternal mortality ratio in developing regions is 14 times higher than in developed countries.[3] Among the direct causes of death haemorrhage is the leading cause of maternal death, followed by hypertensive disorders.[4] Eclampsia is a well-known complication of hypertensive disorders in pregnancy. It is a rarity in the developed countries but has high incidence in developing countries like India.

The convulsions of eclampsia can complicate pregnancy to such an extent that both maternal and fetal life can be in jeopardy. Hence, expert management is the key to prevent maternal morbidity and mortality and improve perinatal outcome. The aim in eclampsia is to control convulsions and to expedite delivery. The superiority and effectiveness of the drug has long been demonstrated by the Collaborative Eclampsia Trial.[1]Toxicity of the drug due to its narrow therapeutic index is a major concern. This limitation poses a great challenge for the medical professional for its judicious use in patient of eclampsia, especially in low resource countries like India. The proposed therapeutic index by Pritchard is based on clinical observations.[5] Therapeutic serum concentrations of magnesium sulphate for the prevention and treatment of seizures have not been vigorously determined and still remain a matter of debate.[6]

Magnesium sulphate can be administered parenterally by either intramuscular or intravenous route. For the intramuscular route of administration, the Pritchard regimen is used. It is noteworthy to mention that this regimen has been formulated as per women of western countries. The Indian women on the contrary have a low BMI as compared to their western counterparts, hence they are at a greater risk of toxicity of magnesium sulphate. Various modifications to the standard Pritchard regimen have evolved around the globe especially in developing countries like Bangladesh and India. In the absence of reliable evidence from randomized trials to guide the choice of regimen for magnesium sulphate when used for women with preeclampsia or eclampsia, clinicians are likely to choose either a regimen they are familiar with, or the one that is recommended in local guidelines. Statistical data on long term basis as such is not widely available.

With the above facts in mind the study was conducted to compare the maternal and perinatal outcome of low dose regimen of magnesium sulphate with the standard Pritchard regimen in antepartum group of eclampsia.

MATERIALS AND METHODOLOGY

Study place-

The study was conducted in the antenatal ward and labour room of D.M.S.G.M.C and Hospital, Purulia, West Bengal. (previously known as D.M.S Hospital for period of 1 year (October 2015 to September 2016).

Study design- Prospective, interventional, randomized, and comparative.

Inclusion criteria-

All antepartum eclamptic patients irrespective of their age & parity.

Exclusion criteria-

Patients having received other anticonvulsants other than magnesium sulphate like diazepam, phenytoin before coming to hospital, patients with intra-partum or postpartum eclampsia, having preexisting seizure disorders, heart blocks or renal failure, who were deeply unconscious with cerebrovascular accident, massive pulmonary edema, associated massive hemorrhage, disseminated intravascular coagulation and shock including sepsis.

Sample size-

86 diagnosed eligible cases of antepartum eclampsia patients divided in two groups A & B (Group A –43/Group B - 43).

Data analysis-

Data was analyzed and entered with help of Epi Info (TM) 3.5.3. EPI INFO is a trademark of the Centers for Disease Control and Prevention (CDC).

Ethical consideration-

The study was conducted after obtaining permission from the Institutional ethical committee of Bankura Samilani Medical College (D.M.C.H was annexed with B.S.M.C.H) & in line with Helsinki declaration of human Ethics.

By using the table of random numbers, every diagnosed eligible case of antepartum eclampsia after taking informed consent was allocated in either Group 'A' or Group' B'. **Group A** (low dose group: A loading dose of 3gm of magnesium sulphate intravenously plus 5 gm intramuscularly [2.5 gm in each buttock] followed by maintenance dose of 5gm i.m. [2. 5 gm i.m. alternate. buttock] every four hours) or **Group' B'**(standard Pritchard regimen: loading dose of 4gm iv plus 10 gm i.m [5 gm.in each buttock] followed by maintenance dose of 10gm i.m [5 gm in alternate buttock] for every four hours till 24 hours after delivery or last convulsion whichever is later.

Toxicity was monitored clinically before administering maintenance dose in both groups. Intravenous labetalol was used as first line antihypertensive unless contraindicated in patients whose systolic blood pressure exceeded 150 mmHg and diastolic blood pressure exceeded 100mmHg.[7]

For recurrence of convulsions an additional dose of 1 gram magnesium sulphate was administered intravenously for the patients of low dose group. For patients of standard Prichard regimen group, an additional dose of 2 gm magnesium sulphate was administered intravenously.

RESULTS

Table 1: Distribution of patients according to parity and treatment regimens (n=86)

Parity	Regimen		Total
	Low Dose	Pritchard	
PRIMI	39(90.7)	36(83.72)	75(87.21)
MULTI	4(9.3)	7(16.28)	11(12.79)
Total	43(100)	43(100)	86(100)

Maximum number of patients in both the groups were primigravidas (90.7% of patients in low dose and 83.72% in standard dose group).

Table 2: Distribution of patients according to 1st convulsion to treatment interval and treatment regimens (n=86)

1st convulsion to treatment interval (in hours)	Regimen		Total
	Low Dose	Pritchard	
0 - 2	23(53.49)	21(48.84)	44(51.16)
2 – 4	14(32.56)	16(37.21)	30(34.88)
4 – 6	6(13.95)	5(11.63)	11(12.79)
≥ 6	0(0)	1(2.33)	1(1.16)
Total	43(100)	43(100)	86(100)

Maximum number of patients in both the groups reached the hospital within 2 hours (53.49 % in low dose and 48.84 % in Pritchard), however, 32.56% patients of low dose and 37.21% of patients in Pritchard group took 2-4 hours to reach the hospital. Only 1 patient took >6 hours to present in the hospital and was in the Pritchard group.

The mean systolic B.P. in the low dose group was 165.07 $\pm$ 8.54 mm of Hg while that in the Pritchard regimen was 163.16 $\pm$ 16.35 mm of Hg. There was no significant difference between the mean systolic B.P. of the two groups. ($p = 0.61$)

The mean diastolic B.P. in the low dose group was 99.40 $\pm$ 9.61 mm of Hg while that in the Pritchard regimen was 100.79 $\pm$ 10.52 mm of Hg. There was no significant difference between the mean systolic B.P. of the two groups. ($p = 0.53$)

The mean platelet count on admission was 1.95 $\pm$ 0.63 lakhs in the low dose and 1.81 $\pm$ 0.56 lacs in the Pritchard group. There was no significant difference between the mean serum creatinine of the two groups. ($p = 0.28$)

Only 4 patients (9.3%) in the low dose and 3 patients (6.98%) in the Pritchard group had an abnormal coagulation profile on admission. Corrected chi-square test showed that there was no significant association between coagulation profile of the two groups. ($p=0.69$)

3 patients (6.98%) in both the groups had an abnormal liver function test on admission. Status of LFT was in equal proportion in two groups.

Table 3: Distribution of patients according to Bishops score and treatment regimen (n=86)

Bishops score	Regimen		Total
	Low Dose	Pritchard	
Favorable	25(58.14)	28(65.12)	53(61.63)
Unfavorable	18(41.86)	15(34.88)	33(38.37)
Total	43(100)	43(100)	86(100)

58.14% of patients had a favorable Bishops score in the low dose group as compared to 65.12% in the Pritchard group.

Table 4: Distribution of patients according to labour and treatment regimens (n=86)

Labour	Regimen		Total
	Low Dose	Pritchard	
SPONTANEOUS	14(32.56)	6(13.95)	20(23.26)
INDUCED	18(41.86)	28(65.12)	46(53.49)
DID NOT GO INTO LABOUR	11(25.58)	9(20.93)	20(23.26)
Total	43(100)	43(100)	86(100)

25.58% patients in the low dose group and 20.93% patients in the Pritchard group did not go into labour. Maximum number of the patients in both the groups had induced labour.

Table 5: Distribution of patients according to mode of delivery and treatment regimens (n=86)

Mode of delivery	Regimen		Total
	Low Dose	Pritchard	
NORMAL VAGINAL DELIVERY	23(53.49)	20(46.51)	43(50)
ASSITED VAGINAL DELIVERY	2(4.65)	4(9.3)	6(6.98)
CAESAREAN SECTION	18(41.86)	19(44.19)	37(43.02)
Total	43(100)	43(100)	86(100)

Maximum number of patients in both the groups had vaginal delivery (58.13% in low dose and 55.81% in Pritchard group). The caesarean section rates in both the groups were high (41.86% in low dose and 44.19% in Pritchard)

Table 6: Distribution of babies born to antepartum eclamptic patients according to still birth and treatment regimens (n=86)

Still birth	Regimen		Total
	Low Dose	Pritchard	
Yes	4(9.3)	7(16.28)	11(12.79)
No	39(90.7)	36(83.72)	75(87.21)
Total	43(100)	43(100)	86(100)

9.3% patients had still birth in the low dose group as compared to 16.28% of the Pritchard group.

Table 7: Distribution of babies born to antepartum eclamptic patients according to APGAR SCORE at 5 minutes and treatment regimens (n=86)

APGAR SCORE at 5 minute	Regimen		Total
	Low Dose	Pritchard	
≤7	8(20.51)	13(36.11)	21(28.0)
>7	31(79.49)	23(63.89)	54(72.0)
Total	43(100)	43(100)	86(100)

Majority of the babies (79.49%) of the low dose group had a good APGAR score at 5 minutes whereas only 63.89% of the babies in the Pritchard group had an APGAR score >7.

Table 8: Distribution of babies born to antepartum eclamptic patients according to Early neonatal death (death within 7 days of birth) and treatment regimens (n=86)

Early neonatal death(death within 7 days of birth)	Regimen		Total
	Low Dose	Pritchard	
Yes	7(16.28)	8(18.6)	15(17.44)
No	36(83.72)	35(81.4)	71(82.56)
Total	43(100)	43(100)	86(100)

7(16.28%) babies in the low dose group and 8(18.60%) babies in the Pritchard group died within 7 days of birth.

Table-9: Distribution of patients according to recurrence of convulsions and treatment regimens (n=86)

Recurrence of convulsions	Low dose regimen	Standard Pritchard regimen	Total
Yes	2(4.65)	3(6.98)	5(5.81)
No	41(95.35	40(93.02)	81(94.19
Total	43(100)	43(100)	86(100)

DISCUSSION

In the above study, 90.07% and 83.72% eclampsia patient in low dose and standard dose group were primigravidas. This result is in accordance with the study of Jana et al.[8] where 89.7% patients were primigravidas. The mean BMI was 19.38+1.74 in low dose group. The mean BMI was 19.06+2.38 in standard dose group. This observation supports the basis of this study that Indian women have a lower BMI as compared to their western counterparts.

In the present study, 79.07% and 72.09% of patients were unbooked in low dose and standard dose group respectively. In studies conducted by Bangal et al.[9] 90% of cases were unbooked. Similar results were observed in study done by Sahu et al.[10] where 92% of low dose and 84% of standard dose patients group were unbooked. Regular ANC check-up remains the corner stone of the prevention of eclampsia, but ANC facilities are utilized at a very low level in our country subsequently resulting in high incidence of eclampsia.

The incidence of eclampsia increases as term approaches. In our study maximum number of patients in the low dose group were in the gestation period of greater than 36 weeks. In the Pritchard dose group commonest gestation of presentation was 32 weeks to 35 weeks 6 days. The number convulsions in eclampsia have an impact on the feto maternal outcome. Our study, 86.05% (Group A) and 74.42% (Group B) of eclamptic patients had less than equal to three convulsions. In the study done by Bangal et al.[9] 72% cases had less than 3 convulsions. 80% of patients in Jana et al.[8] Study had less than 5 convulsions. Sardesai et al.[11] noted that 89.2% of patients had less than 7 convulsions. The findings of our study correspond to these studies. In above study, the first convulsion to treatment interval was greater than 2 hours for 46.51% and 48.84% eclamptic patients in low dose and standard dose group. Our findings that most of the patients were referred from interior villages is supported by the study of Bangal et al.[9] Sardesai et al.[11]

Recurrence of convulsion was the primary outcome of our study. We observed that 4.65% recurrence of convulsions in low dose group as compared to 6.98% in standard Pritchard regimen group. The recurrence rate of convulsions in the low dose group in Sardesai et al.[11] Bangal et al.[9], Jana et al.[8] was 7.89%, 8% and 6.1% respectively.

Toxicity was monitored clinically in our patients. The loss of patellar reflex was lower in low dose group as compared to standard dose group although the difference was not significant. In our study, only 1 patient in low dose had loss of patellar reflex as compared to 4 in standard dose group. The results in our study are corresponding to results of Sahu et al[10]and M. Sahu et al.[10]noted that only 4 patients developed loss of patellar reflex in low dose as compared to 11 patients in standard dose group. The difference was not found to be statistically significant.

In above study, 53.49% of patients in low dose and 46.51% patients had normal vaginally delivery. 4.65% of patients in low dose and 9.3% patients in standard dose group had assisted vaginally delivery. The caesarean section rate in our study was 41.86% in low dose and 44.19 % in standard dose group. Fetal distress was the most common indication of caesarean section in our study. Our findings are consistent with the findings of the CET,[1] in their study the caesarean section rate was 66.2% and 72.5%in the eclamptic patients of the two groups of magnesium sulphate randomized before delivery. The duration of 1st stage and second stage was comparable in both groups. Only 2 patients had a duration of labour of more than 8 hours in low dose and 3 patients in standard dose group.

The Apgar score of ≤7 at 1 min in our study was noted as 43.5% and 55.56% in low dose and standard dose group respectively. In the study by Nautiyal et al.[12] in the low dose group 53.63% newborns had an Apgar score of less than 7 at 1 min. However contrary to our study the Apgar score of ≤7 at 1 min in the study done by Jana et al,[8] and Sahu et al.[10], was observed to be 28.5% and 26.3% respectively with the low dose magnesium sulphate therapy. Sahu et al.[10] in their study also noted a higher number of newborns in the standard dose group with Apgar score ≤7. at 1 min that is 38.9%.The Apgar score ≤7 at 5 min in above study was found in 20.51% and 36.11%in low dose and standard dose group respectively. Our results correspond to the results of Sahu et al.[10] where15.8%and 33.8% of babies had an Apgar score ≤7 at 5 min in low dose and standard group respectively.

There were 7 and 8 early neonatal deaths in above study in low dose and Pritchard group respectively. That corresponds to 16.8% and 18.6% respectively. The high figures can be attributed to significant no. of eclamptic patients with gestation period of <34 weeks. Our results are slightly higher

as compared to the results of Jana et al.[8], who noted 11.6% of early neonatal deaths.

There were no maternal death in either group in our study.

CONCLUSION

The study concluded that low dose regimen has comparable efficacy in convulsion control in women with eclampsia. The low dose group has a better toxicity profile for the patients of antepartum eclampsia and better perinatal outcome as compared to standard Pritchard regimen although the difference was not statistically significant.

Recommendation

A multicentric trial with larger sample size is required to clinically evaluate the efficacy & safety of low dose magnesium sulphate regimen in order to plan for further change in existing treatment protocol of eclampsia patients.

Conflict of interests

In this study there is no Conflict of interests.

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